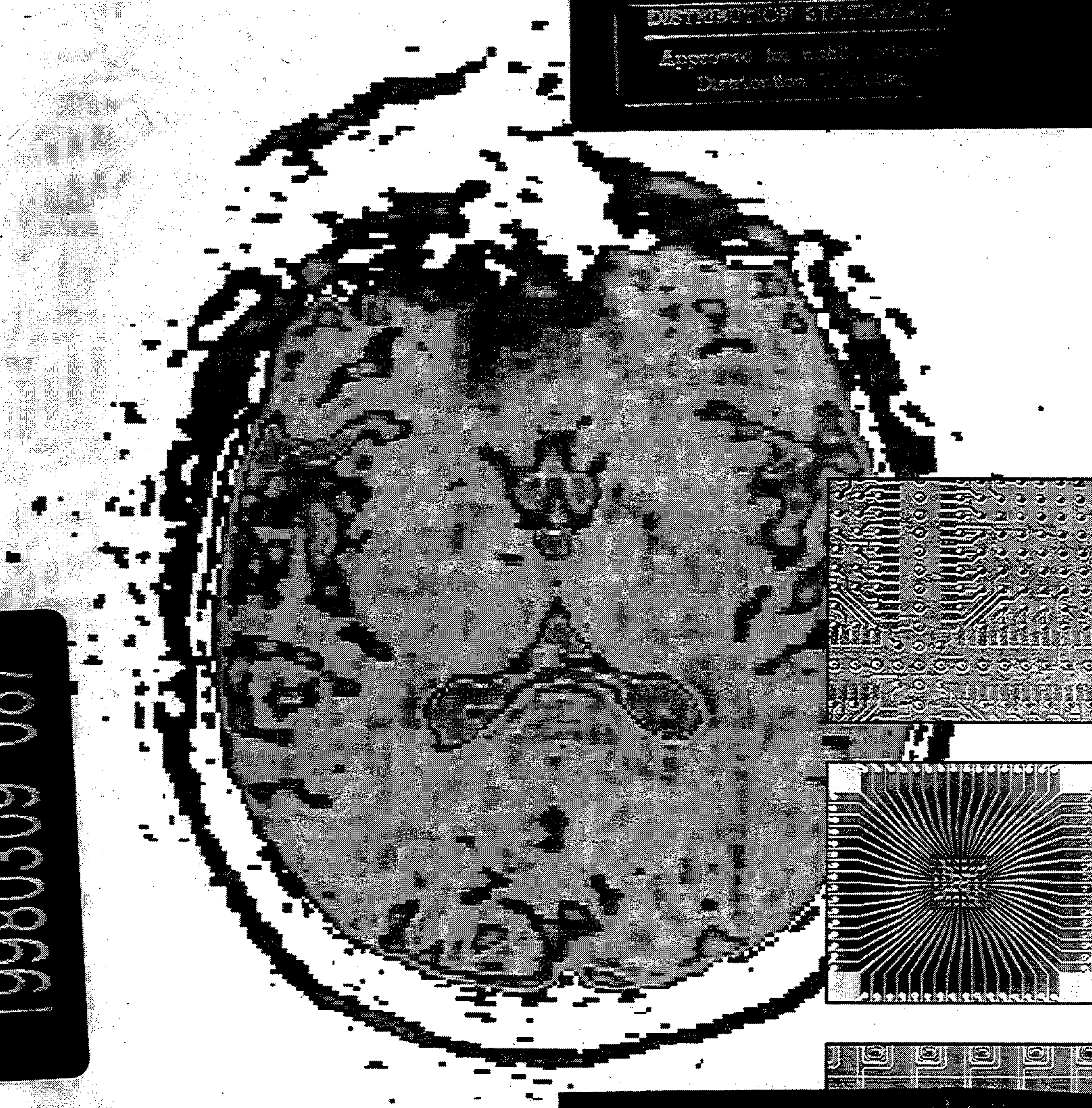
BMDO TECHNOLOGY APPLICATIONS

in biomedicine



Ballistic Missile
Defense Organization

Since 1987, The Ballistic Missile Defense Organization (BMDO) has been committed to the development of innovative technologies that strengthen our nation's defense. In the same spirit of commitment, BMDO is dedicated to technology transfer; moving state-of-the-art military technology from the government into the commercial sector. This report, *BMDO Technology Applications in Biomedicine*, paints more than 60 portraits of actual and potential technology transfers in medicine. From real improvements for mammography to the new vision of optical biopsy, BMDO's investment in advanced technologies has formed the practical base for many medical innovations. While working for a strong national defense, BMDO's technology transfer efforts have made simultaneous contributions to the health of our citizens.

If you would like more information on the technologies or companies featured in this report, please write, phone, fax or e-mail us at:

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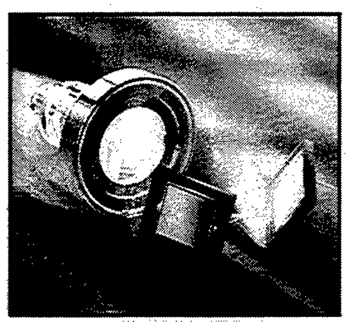

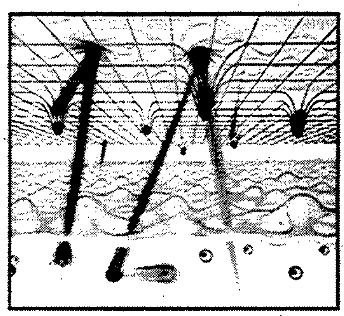

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BMDO TECHNOLOGY APPLICATIONS
in biomedicine

Ballistic Missile
Defense Organization

Foreword

The Ballistic Missile Defense Organization (BMDO) is committed to the development of innovative technologies that strengthen our nation's defense. In the same spirit of commitment, BMDO is dedicated to technology transfer: moving state-of-the-art military technology from the government into the commercial sector. In a rapidly changing world, maintaining technological superiority is a key not only to a secure nation, but to economic stability, job creation, and healthy growth. Moreover, the shrinking government research and development budget makes it more important than ever to exploit the taxpayer investment for multiple uses. Thus we have found that there is an additional benefit to BMDO's investment in technical and conceptual progress: a surprising number of defense technologies have real and diverse applications to medicine and biology. A look at just a few examples of these strange bedfellows will illustrate some unusual yet tailor-made relationships.

■ BMDO's interest in space science and technology led to research in missile tracking and space-docking procedures for orbital vehicles. A laser-based radar tracking method called LADAR resulted from these efforts. LADAR is now enjoying a second career, tracking and locking onto patient eye movements during laser surgery, reducing the risk of complications. Photorefractive keratectomy (PRK) is now a safer and more accurate technique, thanks to this technology.

■ Development of high-temperature superconductors originally addressed such military concerns as highly efficient sensors and high-speed communications. These same materials can be used to sense the faint magnetic fields of the heart, yielding clues to abnormal cardiac rhythms. One day, the electromagnetic patterns of the brain may be studied in the same manner, giving us insight into both normal and dysfunctional cerebral activity.

■ BMDO studies in pattern recognition and high-speed image-processing methods help to quickly identify enemy tanks and differentiate missile threats. An older and craftier enemy, cancer, is now beginning to surrender to the same techniques. Neural networks can be taught to recognize telltale signs of abnormal growth, making earlier detection and, therefore, more effective treatment, possible.

Many other examples of active technology transfer are contained in this report: *BMDO Technology Applications in Biomedicine*. We invite you to sample them, and we welcome any inquiries for more information.

Dwight Duston

Dr. Dwight Duston
Director, Science and Technology, BMDO

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NTTC

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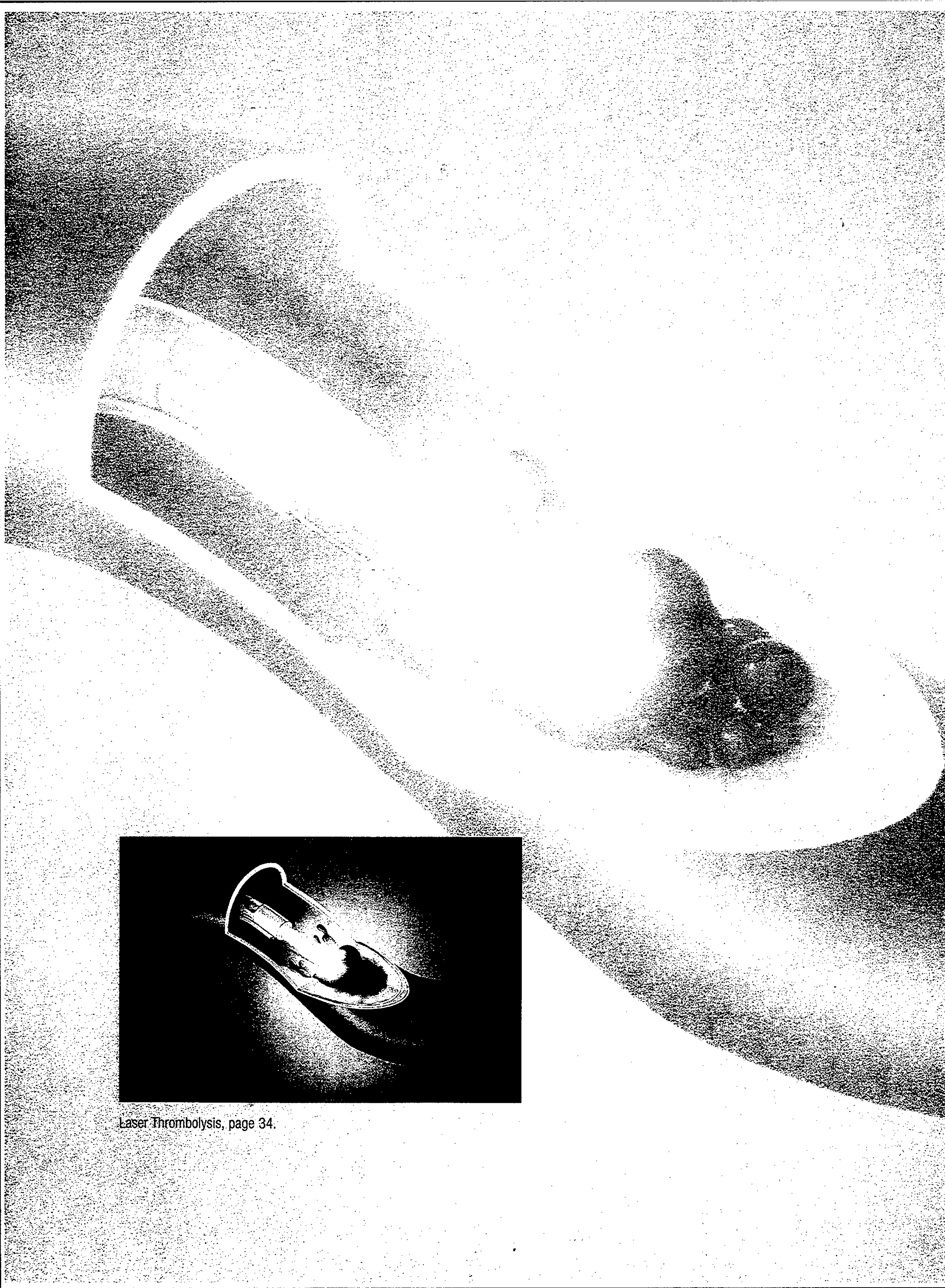

Laser Thrombolysis, page 34.

Introduction

At first glance, it appears unlikely that an agency concerned with warfare and a community concerned with healing would have a single feature in common. While ballistic missile defense does not engage in research aimed directly at medical problems, the technologies involved are frequently similar to those needed by the medical community to identify, diagnose, and attempt to defeat cancer. For example, a missile must be identified quickly and accurately if one is to attempt to destroy the missile before the missile destroys its target. It must be distinguished from other clutter, debris, or decoys moving with and around it; then it must be eliminated, preferably with little collateral damage. A similar level of complexity is encountered in imaging, defining, and targeting cancers and other diseases. However, the task of tracking thousands of incoming missiles pales in difficulty beside the effort to eradicate cancer in multiple sites of the body. In both military and medical terms, it is far better to recognize an event in its earliest stages than to cope with an all-out conflict.

In discussing the development of the atomic bomb in the 1940s, Bernard Baruch observed that "science, which gave us this dread power, shows that it can be made a giant help to humanity." Half a century later, the United States' national security needs that led to the development of the atomic bomb and high-technology delivery systems have changed dramatically and are now being turned toward that " help to humanity." The military technologies developed to protect and defend our nation are being adapted to protect and defend the health and well-being of Americans. Driven by surveillance and target recognition missions, the defense community has invested in research and development of imaging, laser, and other innovative guidance and visioning systems. Today, the resulting technology has found new applications in transportation, environmental monitoring, crime prevention, remote sensing, personal security, civil space programs, and, importantly, in medicine.

This growing research and development partnership between the defense and medical communities could not come a moment too soon, because major enemies of Americans today—dreaded diseases including breast cancer and AIDS—have reached epidemic proportions. The technological advances, resources, talents, and energy from the defense, space, and the intelligence communities that are nearly a decade ahead of medical technological capacity are being brought to the front lines in the battle to improve our Nation's health. The Ballistic Missile Defense Organization (BMDO) is working at the forefront of that effort.

Charged originally with developing the defense technology to safeguard Americans against nuclear attack from abroad, BMDO has helped ensure that our military capacity is the most technologically advanced in the world, bolstering not only our national security, but also our domestic strength economically, industrially, and medically. Over the past decade, BMDO has worked collaboratively with other Federal agencies and with the private sector to translate and transfer many of its sophisticated technologies from defense to medicine. Today, the fruits of BMDO's technological advances are being seen in new techniques in the biomedical research laboratory, at the clinical bedside, and in the operating room.

BMDO funded research for compact linear accelerator technology used in Positron Emission Tomography (PET)—a nuclear-based imaging technology used today to study heart disease, cancer, and that provides us with a window into the living, sleeping, and feeling human brain, helping to unlock the mysteries of mental illness. Laser technologies that today are used in health centers to treat vascular and eye disease, and other disorders come almost directly from BMDO radar-related projects that identify targets and lock missiles onto them.

Additionally, digital imaging, developed for tracking military targets, is making dramatic improvements in the diagnosis of breast and other cancers. Other biomedical applications of sophisticated imaging technologies are being evaluated by BMDO in collaboration with the U.S. Public Health Service's Office on Women's Health and the National Institutes of Health. Not too long from now, the same kinds of simulated environments that teach pilots to fly technologically advanced aircraft will be able to teach medical students about human anatomy using virtual images, to simulate the surgical environment to train physicians in new techniques and equipment without human risk, and to help medical personnel combat disease in rural areas or perform operations and medical procedures under the direction of a surgeon at a distant clinical center.

There can be no greater peace dividend from our national investment in defense than to improve the health of our citizens. This volume, *BMDO Technology Applications in Biomedicine*, speaks to the important ways in which our national investment in defense is being turned to a peacetime benefit that will be counted in millions of American lives saved. I commend the Ballistic Missile Defense Organization for its vision and dedication to this important effort.

Susan Blumenthal

Susan J. Blumenthal, M.D., M.P.A.
Deputy Assistant Secretary for Health (Women's Health)
Assistant Surgeon General
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BMDO and Medical Technologies

The Ballistic Missile Defense Organization (BMDO) has a history of funding basic and applied research in the interest of national defense. Security issues have changed dramatically since the late 1980s, and the function of this agency within the Department of Defense has changed, as well. In addition to defense research, BMDO is committed to technology transfer, moving scientific progress into the commercial sector, and enriching civilian technology, including medical applications.

At first glance it appears unlikely that an agency concerned with warfare and a community concerned with healing would have a single feature in common. In fact, the two are united even in nomenclature. Richard Nixon declared a "war" on cancer during his presidency, a campaign that continues to be waged on many fronts, with technologies that were still in the laboratory 20 years ago. Such language is understandable in the face of a disease that attacks with such devastating consequences. Like an enemy missile, it seems to arrive from nowhere, silently. The terms used in the treatment of cancer even include "tumor kill" references. In addition, national efforts to eradicate infectious disease through immunization have always had a combative ring.

While ballistic missile defense does not engage in research aimed directly at medical problems, the technologies involved are frequently similar to those needed by the medical community to identify, diagnose, and attempt to defeat cancer. For example, a missile must be identified quickly and accurately if one is to attempt to destroy the missile before the missile destroys its target. It must be distinguished from other clutter, debris, or decoys moving with and around it; then it must be eliminated, preferably with little collateral damage. A similar level of complexity is encountered in imaging, defining, and targeting cancers and other diseases. Often, an abnormal cell differs from its normal counterpart in only the subtlest change of architecture or even one mismatch in the genetic code. By the time a collection of cells is sufficiently different from its background to enable detection, the cancer has often metastasized. Metastasis is a truly catastrophic event, which can be likened to a well-armed invasion on multiple fronts. The task of tracking thousands of incoming missiles pales in difficulty beside the effort to eradicate cancer in multiple sites of the body. In both military and medical terms, it is far better to recognize an event in its earliest stages than to cope with all-out conflict.

This metaphoric relationship is also evident in the techniques that medicine and defense use to pursue their very different goals. The physician uses two distinct methods to address the health of the patient: One is preventive health maintenance, the other is active intervention when a problem arises. Both methods require tools to sense and evaluate the status of the patient. The tools can be as simple as a stethoscope, which amplifies sound, to a sophisticated magnetic resonance imaging (MRI) unit, which analyzes the energy emitted from relaxation of spin-aligned protons. The sounds from a stethoscope are processed in an organic computer called a brain, while the signals obtained in MRI are processed by a silicon chip. The fundamental process is the same as that involved in ballistic missile defense: making sense of myriad data points, determining potential dangers, recognizing the stirrings of serious problems, responding to known risk, and avoiding catastrophe.

Like the medical community, BMDO has a directorate to help maintain a "healthy" peace through a strong defense, and to support intervention if the need arises. In surprising ways, the technologies supported by BMDO have much to offer the medical arena. For instance, BMDO computer algorithms that were originally designed to simulate projectile impacts on a surface were later used to help predict laser impacts on a blood clot in a coronary artery. This latter technique, called laser thrombolysis, holds great promise as an alternative therapy for patients who can't tolerate conventional clot-dissolving treatments.

Progress in digital X-ray imaging, a screening and diagnostic mainstay, has been bolstered by BMDO research in silicon pixel development, enabling the development of high-resolution, low-dose radiography. Sensors developed for identifying missiles through plume signatures can also be used in thermographic studies of the human body. High-powered lasers built for directed energy projects have found a wide variety of uses in the fields of tissue ablation (removal) and welding (repair). The list of these technologies is extensive.

Partnership With Medicine

Programs such as BMDO's Medical Free Electron Laser (MFEL) and Positron Emission Tomography (PET) projects have also benefited medicine in general. In 1985, Congress inaugurated the MFEL program, which explicitly stated BMDO's technology transfer goals in medicine. Indeed, the patents and licenses issued as a result of this program have furthered understanding of tissue-laser interactions, photodynamic tissue therapy using photosensitive compounds, light-mediated burn assessments, laser thrombolysis, and noninvasive glucose sensing. MFEL research was conducted nationwide at three laser centers (including Stanford University's top-notch facility), seven medical centers, and three materials science centers (Stanford and Vanderbilt Universities and the University of Utah). BMDO provided more than $50 million to universities and medical research institutions. In 1991, funding for the program continued through the Office of the Secretary of Defense.

BMDO also supported research that led to improvements in PET scanning technologies. In PET scanning a radioisotope is injected into the body, and scintilligraphic images are recorded as the isotope concentrates in target organs and emits radiation from a well-defined locus. Various metabolites can be tagged. For studies of fatty acid metabolism in the heart, for instance, ^{11}C-labeled palmitate and acetate can be used as visualizing media. The use of PET can be prohibitively expensive, reflecting the cost of the accelerator that supplies the very short-lived radioisotopes. To expand on its existing accelerator research, BMDO directly funded development of particle accelerators to be used on-site with stationary and mobile PET units. BMDO's accelerators offer compact and cost-effective ways for hospitals to use PET imaging. Such accelerators may also be useful for production of therapeutic radiopharmaceuticals. One example is strontium-89, an effective palliative for metastatic bone cancer. An accelerator from BMDO's PET project is online at Washington University in St. Louis, MO.

BMDO and Image-Guided Therapy

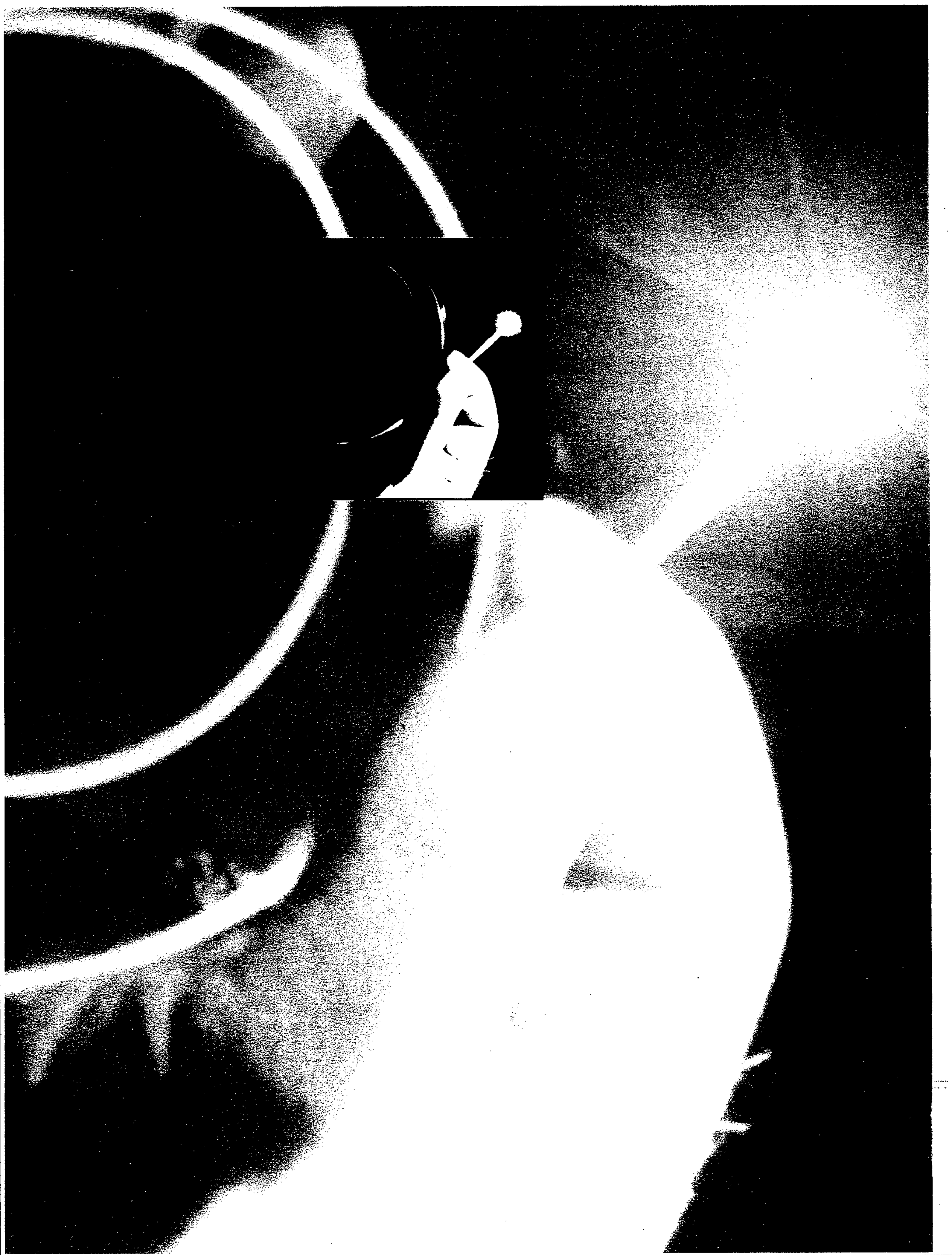
In May 1995, BMDO, the National Cancer Institute, the National Aeronautics and Space Administration, and the Society for Cardiovascular and Interventional Radiology (SCVIR) sponsored a meeting of technical experts and physicians in Bethesda, MD. The gathering addressed current and future trends in medical imaging, diagnostics, and therapies, with an eye to identifying and overcoming technical hurdles in patient care. Many subtexts were evident, including the need for clinical trials to test the efficacy, specificity, and sensitivity of emerging technologies, the necessity for more cost-effective patient care, and a growing demand for noninvasive and minimally invasive procedures. The physicians presented their needs, and the technical community responded by stating their present capabilities and resources. A consensus paper describing the results of this meeting can be obtained from SCVIR.

Synthesis and Collaboration

It is clear that technologists and physicians are attacking related problems but in different ways. Technology engineers are accustomed to stating and then solving well-defined problems. They do not typically work on moving, changing, sloppy, and difficult life systems; they limit their focus sharply and try to consider only those parameters that affect their problem. Physicians, on the other hand, are accustomed to dealing with diffuse, abstract, multivariate problems called human beings. They cannot ethically control every possible experimental variable and they must deal with the unknown to a much greater and more risk-laden degree. It is no easy task to reconcile the perspectives of engineering and medicine, two very creative and resourceful but very different types of livelihoods.

By the same token, the collaboration of many minds with complementary abilities can yield powerful results. Technology advances in traditional nonmedical areas have the potential to contribute even more tools to the practice of healing, and the gap between the technical and medical communities needs to be narrowed. The purpose of this report is to introduce, from the BMDO perspective, a discussion and compilation of BMDO technologies that have a direct or supportive bearing on medical technologies. The substantial investment that has already been made in the defense of the Nation can yield many valuable dividends for the health of its citizens.

This list is by no means all-inclusive, for research continues and products are being developed even as this report is written. However, we trust that this report can serve as a helpful point of departure for those who are interested in leveraging existing and emerging BMDO technologies to improve biomedicine and health care. Many avenues lead to technology transfer; among them are cooperative research and development agreements, joint ventures, technology licensing, and Small Business Innovation Research (SBIR) fund-matching programs. We welcome readers to contact the National Technology Transfer Center for more information.



Existing Technologies

Many well-established medical technologies can benefit from refinement in materials and methods. In medical radiography, for example, resolution of images depends heavily both on how X-rays are scattered in tissue and on technician skill. Film storage leads to scratching and degradation of important baseline imagery. Real-time acquisition of images for patient comfort and for use in surgical guidance are also key factors in controlling radiation exposure and medical costs. Magnetic resonance imaging, a data-intensive image-gathering technique, can benefit from faster data upload and download, higher magnetic field strength, and lower cost. Work continues in the application and fine-tuning of medical lasers. Directed beam therapies and radiopharmaceuticals are fairly recent additions to the proven clinical arsenal and are a rich ground for innovation. Many BMDO-supported technologies can contribute to their impact on health care.

X-Rays

In 1895, a physics professor named Wilhelm Roentgen was experimenting with cathode ray tubes. After one of these experiments, he noted that phosphor screens near the tube were glowing and eventually concluded that the cathode ray tube was responsible. The invisible source of excitation was given the name X-ray, after that favorite term for an unknown, "x." This observation that X-rays could penetrate containers led to the most common of imaging diagnostic procedures.

One hundred years later, one of the biggest improvements in X-ray technology has been the development of computerized axial tomography (CAT). In 1970, X-ray imaging was combined with computer power to create clear, cross-sectional views of an object. The technique was so significant that it won a Nobel prize in physiology for inventors Godfrey N. Hounsfield and Allan M. Cormack of Tufts University. In CAT scans, an X-ray scanner is rapidly rotated around the subject, yielding high-resolution images of the body's interior that often provide more information than conventional two-dimensional X-ray images. In spiral or helical scanning tomography, a recent innovation in this area, X-ray delivery occurs in a rotating spiral pattern, as opposed to the slice-by-slice, conventional CAT scan pattern. Digital image enhancement can be combined with CAT imagery to improve contrast and sharpen detail.

Strengths

Because of its ubiquitous use in rapid imaging of medical problems from broken bones to ulcers, X-ray imaging has become highly available and relatively inexpensive. X-rays have been quantitatively assessed for dosage limits. Angiography and angioplasty require use of X-rays, as do gastrointestinal series, spinal studies, and detection of primary and metastatic cancers. Chest X-rays can be used to confirm diagnoses as diverse as pneumonia, tuberculosis, chronic asbestos exposure, or an enlarged heart. X-ray-based mammography is generally accepted as a screening method for early breast cancer detection.

Limitations

Since X-rays are a source of ionizing radiation and are therefore potentially mutagenic, their use is limited by recommendations for yearly or lifetime exposure. In addition to being a reader-dependent diagnostic art, it is a technique-dependent method. The film images produced by X-ray are gray-scale and could benefit greatly from resolution enhancement techniques or by eliminating film and converting radiation to digital storage (e.g., through a charge-coupled device). Image quality is also partially dependent upon the radiation's penetration of and scatter throughout the tissue, and these phenomena can differ widely, depending on body type, fat percentage, and so on.

Although mammography is an entrenched screening tool for breast cancer, it is still subject to the outcome of various longitudinal studies and debate. There is a consensus that mammography is a reasonable trade-off between radiation exposure and tumor detection for women over 50. For women younger than 50, opinions vary widely because the dense breast tissue characteristic of premenopausal women is difficult to image with mammography. Advances in image enhancement and computer-aided diagnosis can provide answers to help resolve this continuing debate. Current mammography enables detection of abnormalities as small as 5 mm in diameter, as well as submillimeter calcifications that can be indicative of cancer. Except in highly macroscopic conditions, the radiologist looks for changes in successive mammograms, ideally with a baseline image as an initial point of reference.

Digital Mammography Eliminates Film

BMDO Technology Background

BMDO research in industrial radiography led directly to a new method of digitizing images for mammography, including computer-aided diagnostic techniques. As in numerous other labs and companies, the effort is to make mammography a "filmless" experience. This work is supported by a cooperative research and development agreement (CRADA) between Lawrence Livermore National Laboratory (LLNL; Livermore, CA) and Fischer Imaging (Denver, CO).

How It Works

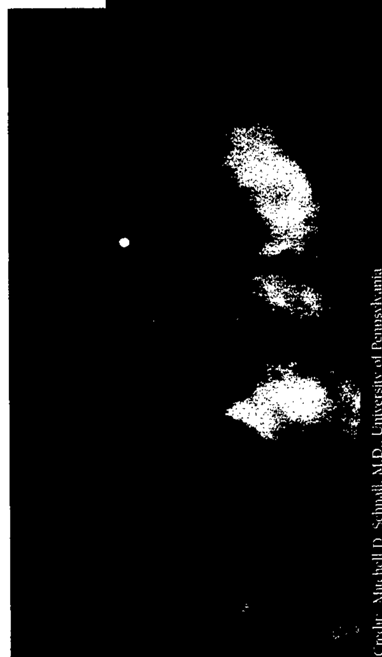
In filmless mammography, the X-rays pass through the breast and into a scintillating material, where they are converted to visible light. The light travels through a fiber-optic reducer, which is a bundle of individual fibers that is stretched so that one end is larger in cross-sectional area than the other. For example, this allows a 2 cm x 2 cm area of breast image to be captured on a 1 cm x 1 cm charge-coupled device (CCD). It currently takes an array of about 20 CCDs to record a full breast image. Fischer's device takes about 4 seconds to acquire an image.

Potential Use to Medicine

Researchers hope to build a system that will identify all of cancer's warning signs, making computer-aided diagnosis a viable commercial option. A dental apparatus to screen images of teeth for signs of decay is also a possibility. Researchers at LLNL are working on programs to recognize and flag danger signs in digital mammograms so that cancer can be detected and treated even at its earliest stages. In particular, they are developing an algorithm by which the computer will spot microcalcifications, which appear as tiny specks scattered across the image and are often missed by the human eye. The same program will then flag possible trouble spots for further scrutiny by radiologists.

Product Status and Availability

Under a CRADA signed by LLNL and Fischer Imaging in October 1993 a complete digital mammography system will be designed from the floor up, including the means to capture images electronically and send them directly to the computer. A working prototype is expected by 1996.



▲ White dot on mammogram indicates palpable abnormality.

Fiber optics and new image acquisition materials can make mammography a filmless experience.

New Technique Peers Into Bones and Teeth

Conventional X-ray of rheumatoid arthritic swelling in a hand.

BMDO Technology Background

A new and powerful X-ray technique developed at Lawrence Livermore National Laboratory (LLNL; Livermore, CA) and Germany's University of Dortmund allows researchers a three-dimensional look at the interior of materials such as industrial ceramics, metal matrices, bones, and teeth. BMDO-sponsored research at LLNL and Sandia National Laboratories led to the development of this technique, called X-ray tomographic microscopy (XTM). XTM is similar to CAT scanning and has a resolution of about 1 micron, which is roughly 500 to 1,000 times sharper than CAT.

How It Works

In the XTM apparatus, X-ray photons pass through a sample positioned on a rotating stage. They are then converted to visible light on a scintillator screen and imaged with a two-dimensional CCD detector. The CCD allows multiple, contiguous tomographic cross sections to be collected at the same time, so the volume can be viewed in cross section by slicing through the structure in any planar direction. Such planes can be combined to produce a three-dimensional rendering of the structure, emphasizing material of either higher or lower density. A strain microscope attachment developed by Sandia allows examination of structures under load.

XTM can use either synchrotron-produced or conventional X-ray sources but a synchrotron radiation source results in the highest resolution. XTM can obtain 2,000 image "slices" in less than an hour.

Potential Use to Medicine

XTM is currently being used to study the microstructure of bones and teeth. With a grant from the National Institutes of Health (NIH) and the National Institute of Dental Research, researchers are using XTM to map mineral distribution in teeth. This research can shed light on how dental caries (cavities) form and may lead to improved filling composites.

Pharmaceutical firms, such as Eli-Lilly, Procter and Gamble, and Merck, are interested in using XTM in their drug research.

XTM can also image the lacy, inner matrix of bone and reveal how bone loss and bone formation occur. An understanding of these processes can help researchers devise new remedies for osteoporosis and arthritic bone degradation, and perhaps help to explain how estrogen retards bone loss.

Researchers are also looking at the utility of XTM in catheterization procedures such as balloon angioplasty. The main obstacle to this use is the large size of synchrotrons needed as an X-ray source.

Product Status and Availability

In vivo studies in bone loss are now being conducted with XTM at the University of California, under a 3-year NIH grant. Drug companies such as Roche Bioscience are actively working with LLNL, using XTM to determine how steroidal drugs break down bone. Other pharmaceutical firms, such as Eli-Lilly, Procter and Gamble, and Merck, are also interested in using XTM in their drug research. Dr. John Kinney, principal investigator at LLNL, is interested in collaborative research proposals from other companies, as well.

From Infrared to X-Ray

BMDO Technology Background

NOVA R & D (Riverside, CA) is working on a scanning digital mammography unit with higher spatial resolution, lower radiation, and better display with higher contrast than present mammography methods. The key to the system is a silicon pixel detector (SiPD) developed for BMDO systems at Hughes Aircraft Company (El Segundo, CA). Hughes developed SiPD technology for use in infrared sensors. NOVA proposed a modification of these silicon pixel devices for X-ray detection in digital mammography. The X-ray detector was an adaptation of the infrared sensor technology.

How It Works

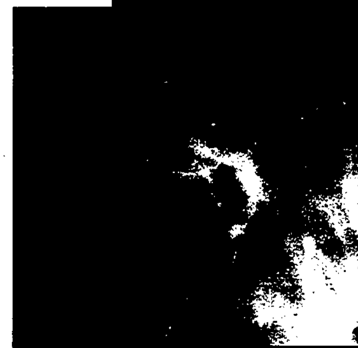
SiPD places thousands of individual detector pixels in a single semiconductor substrate, which is connected to a front-end readout electronics chip with a time-delayed integration-charge-coupled device (TDI-CCD) function. The sections have matching pixel geometry and are electrically connected through an indium bump bonding technique, which allows each diode to be directly connected to its readout electronics. This setup in turn enables the fabrication of small-capacitance and low-noise detectors. NOVA's systems could also be used for bone densitometry and panoramic dental X-rays.

Potential Use to Medicine

Dr. Martin Yaffe of the Sunnybrook Health Science Centre in Toronto has been collaborating with NOVA. Dr. Yaffe's research in digital mammography has helped NOVA in its quest to reduce radiation dosage, eliminate the need for a grid (used in conventional systems to reduce scatter), improve image resolution, and produce a filmless X-ray that can be electronically stored and transmitted. Dr. Yaffe is currently using a scanned slot system with a detector array that is 50 to 500 x 5,000 to 6,000 pixels. The detector is moved in one direction as X-rays are delivered to the breast, capturing incident radiation one section at a time; it takes 1 to 5 seconds to complete the scan. The sections are overlapped to create an image of the whole breast.

Product Status and Availability

NOVA plans to have a prototype silicon-pixel based mammography unit by 1997.

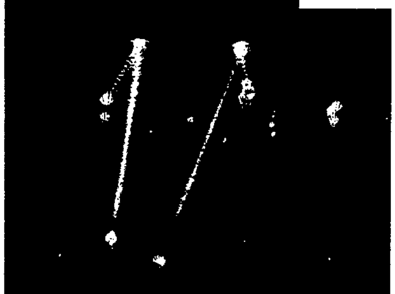


Credit: Dr. Martin Yaffe

▲ An image obtained with a CCD-based scanning digital mammography system.

Silicon pixel technology will offer high-resolution, low-dosage mammography.

Novel Materials Aid in Mammography Design



Quantex Corporation's ET®s can help increase sensitivity of mammographic images.

BMDO Technology Background

In part through a BMDO Phase I SBIR contract, Quantex (Rockville, MD) developed light-trapping materials for use in high-speed optical computers. Military areas impacted by this technology are missile identification, high data transfer rates, and massive optical storage capacity. Quantex named these materials ET®s for their electron-trapping ability.

How It Works

ET® storage media are composed of alkaline-earth chalcogenides doped with two or three rare earth elements. Visible and non-visible light (sunlight, fluorescent light, X-rays, etc.) energizes the ET® by raising the energy levels of electrons in the first dopant. These electrons decay into the ground state of a second dopant material, where they are "trapped." They can be held in this stable state for periods of several years or more. When exposed to infrared (IR) light, however, the trapped electrons again are raised to a higher energy state and then decay back to the ground state of the first dopant. As they decay to the original ground state, the electrons give off light (photons) in the visible spectrum. The emitted photons have an intensity that corresponds to that of the initial incident photons. For this reason, ET®s are excellent alternatives to conventional X-ray film; Quantex has created compounds that store X-ray images, which are also released when acted upon by incident IR light.

Potential Use to Medicine

Light-trapping materials lend themselves to the capture of incident radiation, for visible light as well as for X-rays. Quantex's material innovation is useful in many types of optical and imaging applications and has excellent potential to improve X-ray capture and to eliminate the "noisy" step of film processing. They can also retain trapped electrons for long periods, which translates to long-term data storage. ET®s are also intrinsically compatible with digital imaging and storage methods, which is important because digital images can be electronically transmitted and stored in areas remote to the image-acquisition site.

Quantex is making a substantial effort to improve the state of the art in mammography. By leveraging the company's ET®s into a solid-state mammography unit, the company plans to build a system that increases contrast sensitivity tenfold, eliminates film processing, and incorporates computer-enhancement of images. These improvements can lead to earlier detection of breast cancer, reduced radiation exposure for patients, and a standardized method for image capture. Images acquired in this fashion can also be transmitted to remote areas over standard communication lines, furthering telemedicine capabilities.

Light-trapping materials can serve in computing, recognition, and visualization tasks.

Product Status and Availability

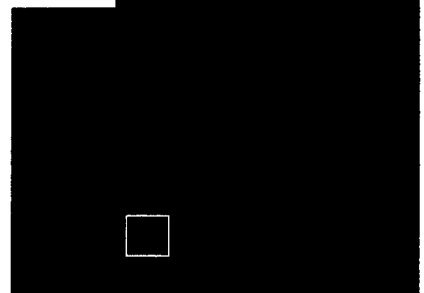
Quantex has received other SBIR awards for a filmless, digital, dental X-ray imaging system; a filmless mammography system promising superior resolution, dynamic range, and cost efficiency; and a new radiographic imaging system for protein crystallography analysis. The company has licensed a life-sciences company for radio- and chemiluminescent-tracer DNA imaging. Quantex has also licensed technology to another company engaged in nondestructive evaluation of nuclear power plants and the gamma/X-ray imaging field.

Defense Technology Targets Medical Imagery

BMDO Technology Background

In April 1995, Rose Health Enterprises (Denver, CO) and Lockheed Martin (Denver, CO) formed a company called MedDetect, LLC, to convert defense technology to medical image analysis applications. Lockheed Martin has had several contracts with BMDO to develop target recognition and acquisition technology; target scene generation software and optical components for rapid data processing are among these technologies. According to E. Michael Henry of Lockheed Martin, the target acquisition methods used for both military and medical applications are state of the art.

MedDetect's initial work is focused on optical processor capabilities in mammography. Fast optical computing of complex algorithms, as well as automated electronic analysis of mammogram images, are expected to make screening methods faster and more accurate.



▲ Bold white square indicates "region of interest," or possible abnormality, on this mammogram.

How It Works

The techniques used by MedDetect are a hybrid of optical and digital processing. An optical correlator uses a low-power laser and lenses to examine the mammographic image. The optical correlator uses photons instead of electrons to perform the calculations necessary to detect an abnormal feature. This information is then transmitted to a computer that uses neural network software to learn the specific attributes of breast abnormalities. The "learned" information is stored and applied to new images. This technology has been successfully demonstrated on military helicopters for identification of camouflaged ground vehicles.

Potential Use to Medicine

Approximately 90 percent of screening mammograms are negative; if some of these negative images can be assessed quickly, the physician can use the time saved to carefully examine and evaluate the remaining images. In addition, pattern recognition makes screening a more powerful tool by automatically tagging abnormal image attributes. In preliminary tests based on historical mammographic images, the technology has already identified a cancerous breast lesion that was not apparent for another year by conventional methods.

Optical processing can speed up image acquisition for mammography.

Mammography was estimated to have accounted for $1 billion in health care costs in 1994. MedDetect aims to reduce mortality through earlier detection, and to reduce mammography costs by speeding analysis and diagnosis.

This system will also be perfectly compatible with filmless digital mammography that is under development in companies such as Fischer Imaging (Denver, CO), NOVA R & D (Riverside, CA), and ThermoTrex (San Diego, CA). The X-ray image can undergo lesion analysis in less than a minute, transmitted to another radiologist for a second opinion, and then digitally stored in a centralized location. The latter capability is also important for baseline analysis of, quick access to, and comparison of images.

Product Status and Availability

Both Rose and Lockheed Martin are providing seed money for MedDetect and plan to raise additional private capital. A prototype should be available within 18 to 24 months. MedDetect also expects to use these optical processing methods to improve cancer detection in chest X-rays, Pap smears, and other cytological analyses.

Digital Imagery Outperforms Conventional X-Ray

Conventional mammogram compared to digital image.

BMDO Technology Background

Using advanced imaging techniques and digital technology originally developed for the Strategic Defense Initiative, ThermoTrex Corporation (San Diego, CA) has made a major contribution to the development of digital mammography. Through its LORAD division, ThermoTrex has built a prototype device that outperforms conventional mammographic imagery by expanding the nuances of gray-scale and by better detecting microcalcifications that can signal the presence of cancer. In November 1993, LORAD demonstrated the first full breast digital imaging system, which showed superior image acquisition, especially for the dense breast tissue of young women, for whom conventional mammograms are hard to read. In addition, LORAD uses this same digital technology in StereoGuide™, a stereotactic device, for positioning the breast for fine-needle biopsies and aspirations. This device provides accurate and minimally invasive investigation of breast tissue, and is being marketed successfully in the United States.

How It Works

Instead of using hard-to-store and scratch-prone X-ray film, ThermoTrex's prototype records X-rays in digital form using a charge-coupled device (CCD). In near-real time, an image of the breast is collected by the CCD, can be digitally enhanced if desired, and stored electronically. The image can be displayed on a computer monitor or printed on conventional film and also can be relayed to remote sites for consultation between radiologists. The digital format of the information means that computer-aided diagnostic algorithms can be used to analyze the mammogram.

For its stereotactic device, LORAD employs a 25 cm^2 field-of-view X-ray receptor, which can be used to view small areas of the breast targeted for fine-needle biopsy. By contrast, the full breast imager records a 6.75 cm x 6.75 cm section of the breast. The camera sequentially images 12 overlapping sections of the breast, and the resulting data is "stitched" to yield a seamless picture of the full breast. These electronic stitching methods were developed by the National Aeronautic and Space Administration for the Voyager spacecraft. The final image is in the form of a 3,072 x 4,096 pixel matrix, or 24 megabytes of data.

Superior images for accurate diagnoses and surgical guidance.

Potential Use to Medicine

The use of digital methods in mammography makes possible electronic transmittal and storage of X-ray images, direct application of computer-aided diagnostic algorithms, sharper and more accurate images for better lesion detection, and reduced exposure to radiation, all of which translate to early cancer detection, reduced risk, and improved survival.

Product Status and Availability

The digital mammography unit is still under development. A prototype device is installed at the University of California at San Diego's Center for Women's Health, where it has imaged 25 volunteers during 1995. Second-generation prototypes being installed at the University of Virginia (Charlottesville, VA) and at the University of California at Los Angeles will be used to collect patient data for Food and Drug Administration approval requirements. Images from the unit were showcased at the December 1994 meeting of the Radiological Society of North America and were favorably received by physicians from some of the country's premier oncology centers.

Magnetic Resonance Imaging and Related Technologies

Nuclear magnetic resonance, or NMR, was first applied to medicine in 1977 by Dr. Raymond Damadian of the State University of New York's Downstate Medical Center (Brooklyn, NY). NMR uses a superconducting magnet to align the spin states of hydrogen atoms in cells of the body. When the magnet is turned off and the atoms "relax" to their normal alignment, they emit measurable frequencies. These frequencies are computed, using powerful algorithms, and an image is generated from the results. Protons that are tightly bound within molecules, such as those in bone, emit weak signals, while protons in aqueous environments emit strong ones. Magnetic resonance imaging (MRI) is a direct descendant of NMR.

Strengths

Because MRI produces no ionizing radiation, the entire body can be safely viewed without concern for exposure time. MRI can be augmented with injectable paramagnetic contrast agents such as gadolinium. This method is very useful in brain imaging, and to a lesser extent, in spinal studies. A recently developed investigative method for lung imaging with MRI involves the use of an inhaled gas. MRI has some value in assessing cancer, especially in investigations of disease recurrence, but it is not yet regarded as a reliable screening tool. It is especially good for imaging soft tissues and shows promise for blood flow studies.

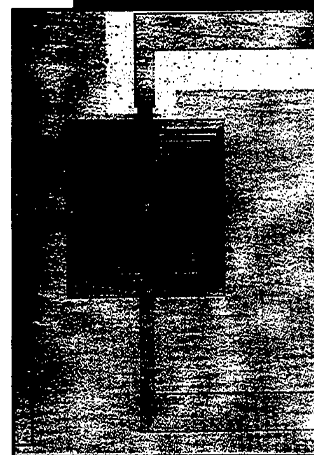
Limitations

Despite its promise of accurate, noninvasive imaging, MRI is underutilized. The equipment is very expensive (about $1.5 million per unit cost) and patient throughput is slow. These costs, which are tied to throughput and materials, could be ameliorated with smaller equipment and high-temperature superconductors (i.e., more powerful magnets of smaller size). Patients with cardiac pacemakers and implanted metallic prostheses can't be imaged with this technique. Another limitation is that the tube in which the patient is placed often elicits feelings of claustrophobia, which has turned out to be a surprisingly significant problem. Children usually have to be sedated for MRI. Open magnet units are becoming increasingly available, but at the expense of magnetic field strength, according to one researcher.

MRI, along with X-rays, computerized axial tomography (CAT), and ultrasound, represents a complement in the field of imaging. It images some anatomical features very well, but fails, for instance, in visualization of bone. It is an important method for visualizing tumors in parenchymal tissue, such as the liver. A 0.4 T field MRI machine requires up to an hour to create a good image. While MRI is promising for diagnosis of breast, prostate, and other cancers, its capacity to examine stages of known cancers must be evaluated further before it can be used for detection. Some studies in prostate carcinoma find that MRI misses up to 40 percent of cancers, and has a lower limit of detection of 5 mm.

Cost is an important issue in this era of declining resources and the limits of third-party payers. Reducing the size, but not the strength, of the magnet, and increasing the speed of throughput, would lower the prices of the scans. Helium-based superconductors are expensive, and helium itself boils away rapidly. Hence, high-temperature superconductors would be useful in driving down costs as well. Data upload and download are also time-consuming and inefficient, and comprise a good deal of the preparatory stages for MRI. Hence, software design and the use of parallel processors are valuable to this technology.

High-Temperature Superconductors Instrumental for MRI



▲ A high-temperature SQUID magnetometer.

BMDO Technology Background

Conductus (Sunnyvale, CA) has performed a variety of BMDO-related research projects on high-temperature superconducting (HTS) materials. As a well-established manufacturer of magnetic sensing instrumentation, the company has been able to apply its innovations to components for NMR equipment, MRI, and magnetic sensing of the heart.

How It Works

MRI applications. Conductus uses a proprietary thin-film technology to process HTS products based on yttrium barium copper oxide (YBCO). YBCO is the only material suitable for fabricating electronic circuits that contain multiple layers of superconductors and other thin-film components. Operation at 77 K means that liquid nitrogen can be used as a coolant. For MRI applications, radiofrequency receivers that are currently made of copper coils can be replaced by superconducting receiver coils, increasing signal-to-noise ratio by a factor of two in some cases. This change is especially important in low-strength MRI fields (based on lower cost magnets), where weak fields mean weak signals. Superconducting coils could boost the performance of these machines by improving image quality and reducing measurement time.

Magnetic field sensing. Compared with the rest of the body's low current operations, the heart is a highly electric organ. Its faint magnetic field (about 100 picoteslas) can be measured with superconducting quantum interference devices (SQUIDs), the most sensitive magnetic sensors known. When arranged in arrays, SQUIDs can provide an image of the heart's magnetic field and yield clues to abnormal conduction patterns that are the basis of some heart arrhythmias (abnormal rhythms). About 3 million persons are treated for arrhythmias each year in the United States.

Magnetic resonance spectroscopy. Magnetic resonance spectroscopy (MRS) is similar to MRI, but instead of being tuned to the relaxation signatures of a proton, the spectrometer is tuned to a significant tissue element, such as an isotope of phosphorus in cellular adenosine triphosphate (ATP). ATP is an indicator of energy consumption in a cell, and some studies suggest that tracking its usage in cells is valuable in judging tumor response to chemotherapy. Similarly, by tuning to an isotope of oxygen or carbon, other compounds can be "viewed." Many animal studies are ongoing in this area. Receivers for this technology must be even more sensitive than for conventional MRI, because the "noise" level in these tissue studies is considerable. HTS receivers would be helpful in increasing the utility of MRS.

Medical educators may be interested in Conductus' Mr. SQUID™, an HTS product.

Potential Use to Medicine

A simple component change in an MRI machine, involving the replacement of a receiver coil, can greatly improve a valuable imaging modality. Use of low-field machines can continue without the current drawback of slow, weak signal acquisition and inferior image quality. Furthermore, Conductus' development of a noninvasive device for assessment of cardiac conduction patterns will bring yet another benign diagnostic tool to medicine.

Product Status and Availability

Conductus is a leader in superconductive electronics. The company manufactures and sells both high- and low-temperature SQUIDs for nondestructive sensing and other test applications. HTS receiver coils for MRI and NMR, as well as the SQUID-based cardiac magnetic field sensor, are in the product development stage. Conductus is also codeveloping a coil with Varian for a standard NMR instrument, which will be available in late 1995.

Medical educators may be interested in Conductus' Mr. SQUID™, a sensitive superconducting magnetometer for the physics laboratory. This HTS product is the first commercial use of liquid nitrogen-cooled SQUID technology.

Real-Time Processor Speeds Up Imaging Time

Colorized MRI image of brain done on ImSyn™ breadboard.

An optical processor can reduce motion artifacts and perform pattern recognition tasks.

BMDO Technology Background

Essex Corporation (Columbia, MD) is marketing a high-speed processor that could significantly cut data processing time in MRI, ultrasound, and other diagnostic examinations. It can be a freestanding or an extremely powerful add-on computer that assists the workstation by forming precise images in fractions of a second. The ImSyn™ processor is designed to handle various types of imaging, even those not uniformly sampled on a rectangular grid, such as MRI. The optoelectronic processor gives real-time processing speed to polar, spiral, or any arbitrary sampling sensor. The equipment is small and lightweight, runs on low power, and is not difficult to use.

How It Works

The processor takes data directly from any sensor, such as an MRI coil, and sends real-time imaging to the workstation for display. Standard workstation software performs image enhancement and manipulation, if desired. The system is a two-dimensional real-time Fourier transform processor with high-speed input/output that uses optoelectronic technology for speed and flexibility. Data received from the sensor are formed into images in the processor, and these images are then sent to the image analysis workstation. The pattern recognition option results by forming the complex correlation with an appropriate pattern in a database. Both processes require a minimum of support software on the host workstation.

Potential Use to Medicine

The ImSyn™ processor allows physicians to see a target tumor or other anatomical feature precisely in real time, while its high speed reduces motion artifacts that can blur images. The processor can also perform complex correlations, used in pattern recognition, with high precision. In terms of better imaging speed and the potential for computer-aided diagnosis, the processor fits in well with the projected future of medical imaging.

Product Status and Availability

The system interfaces with standard, low-end workstations such as Sun Sparc, DEC, Hewlett Packard, and Silicon Graphics. Adding the Essex processor has the potential to improve patient throughput by drastically reducing the time currently spent downloading software and preparing to receive image information from the sensor. Essex is offering preproduction units to developers; breadboard versions have been functioning since 1991.

3-D Computer Manages Complex Imagery

BMDO Technology Background

To develop technology that will allow almost instant target recognition, BMDO funded computer projects that would yield very high speed computers small enough to put on board a spacecraft. In response, Hughes Research Laboratories (Malibu, CA) is developing a very powerful small computer with potential applications that include image processing and two-dimensional signal processing. Hughes satisfied the BMDO requirement for weight and space by stacking 15 128 x 128-element, monolithic wafers in a fine-grained (complex) architecture. The design accommodates the massive data throughput generated by such procedures as MRI.

How It Works

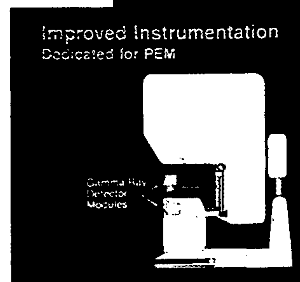
The horizontal, two-dimensional array of processors work in lockstep while executing a common program. Functional subunits of each processor are distributed vertically. Signals travel locally within each wafer of the stack through conventional aluminum and polysilicon conductive layers. Signals are passed vertically through the stack by way of bus lines composed of feedthroughs (signal channels through the wafers) and microridges (signal channels between the wafers). All processors forming the cellular array are identical since they are composed of the same number and type of functional subunits. Computers can be assembled with computational capabilities tailored to specific applications, but the family of computers shares common architecture, instruction set, and input/output structure.

Potential Use to Medicine

Fast image processing depends on fast computing times and powerful software. Hughes' computer can address these needs in relation to diagnostic imaging. Like those destined for aircraft, medical computers that generate images from MRI, PET, and other imaging diagnostic procedures must be very robust in terms of processing ability, very fast, small, and inexpensive.

Product Status and Availability

The three-dimensional computer boasts modular construction for flexibility, fault tolerance, small size, low power consumption, and low manufacturing cost. Hughes is seeking technology partners or licensing opportunities for this promising technology.



Credit: National Cancer Institute, Bethesda, MD

▲ 3-D computing can improve resolution for many types of imaging.

Hughes is seeking technology partners or licensing opportunities for this promising technology.

Ultrasound

Now a standard imaging technique for prenatal imaging, ultrasound (US) uses ultrahigh frequency sound waves (over 20 kHz, but more often well into the MHz range) to bounce signals off anatomical features.

Strengths

Fetal imaging and echocardiography (imaging the heart) are well-established US techniques. Examination of the liver, bladder, kidney, aortic features, and even the eye, can also be accomplished with US. Advances in software and processing times have made possible three-dimensional reconstruction of US images, and research is being conducted in the assessment of fetal craniofacial abnormalities, diagnosis and presurgical staging of prostate cancer, differential diagnosis of mammogram-detected breast abnormalities, and guidance for tissue sampling. Doppler-flow US, incorporating velocity measurements of liquid flow, has proven efficacious for detection of deep-vein thrombosis (clotting) and peripheral vascular disease. US is gaining acceptance as an image guidance technique for both prostate and breast biopsy.

Limitations

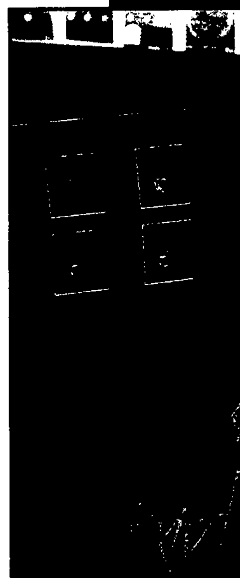
Some US imaging must be conducted though a "water window," often requiring patients to retain a full bladder for long periods. This requirement can be quite uncomfortable, especially for pregnant women and for men with prostate disease. Some US breast imaging methods once required viewing the breast on a water-filled bag, entailing in some cases awkward anatomical placements. Innovations in this area have eliminated some of these drawbacks. Like MRI, US is currently seen as inadequate for prostate cancer screening. US is therefore used along with other diagnostic methods such as prostate-specific antigen (for prostate cancer), human chorionic gonadotrophic hormone levels (for determination of gestational age in pregnancy), and other imaging modalities. Improvements in signal extraction and amplification, as well as integration with volume-filling computer models, can help expand US's clinical role.

Noninvasive and Novel Method for Visualization

BMDO Technology Background

ThermoTrex Corporation (San Diego, CA) has performed extensive research for BMDO in the area of advanced imaging and digital technologies. Some of this work eventually translated to a breakthrough digital mammography prototype system, which will be sold through LORAD, a division of ThermoTrex. ThermoTrex itself has also made some significant strides in ultrasonic imaging techniques including Sonic CT (computed tomography) which is suitable for breast imaging. Sonic CT holds promise for examining breast abnormalities that are not readily apparent with X-ray mammography. This technology also does not require compression of the breast, which can be painful.

Doppler CT, a variant of Sonic CT, has the potential to image blood vessels in three dimensions, assess velocities of blood flow, and assess patients with known or suspected vascular disease. For example, blocked flow in the arteries of the legs, or in the carotid arteries, which supply the brain, can be examined with this method.



▲ Sonic CT is an innovative direction in breast imaging.

How It Works

In both Sonic and Doppler CT, ultrasound signals are converted into digital images of anatomical features and can be electronically processed and stored, just as X-ray images are manipulated in what is now "conventional" CT. Sonic CT uses low-frequency ultrasound to produce cross-sectional slices of the breast, acquiring images in near-real time.

Doppler CT can measure the velocity of blood coursing through vessels. Blood flows more quickly through a passage narrowed by plaque or scar tissue than through an unobstructed blood vessel with a wider diameter. So, by comparing the speed of blood flow in adjoining areas of an artery, it can be determined whether a blockage exists in that artery. While current Doppler methods offer speedy and safe imaging, they do not offer the resolution of angiographic techniques. Doppler CT can greatly improve image resolution, although perhaps not to the fine level of contrast methods.

Ultrasound can provide breast images that are not attainable with X-rays.

Potential Use to Medicine

Ultrasound requires no ionizing radiation, so its use needn't be curtailed by exposure worries. Sonic CT has the potential to spot breast abnormalities that are not associated with microcalcifications. It would be valuable in assessing such conditions as fibrocystic breast disease ("lumpy" breast disease, most often benign) and could help reduce the number of breast biopsies, 80 percent of which are negative.

Doppler CT represents a step forward in the state of the art in Doppler imaging, and can be useful in monitoring postoperative patients who are at risk for blood clot formation. It can also be used for better measurement of carotid artery diameters (a significant concern in the aging population) and in evaluating patients with peripheral vascular disease, or "hardening" of the blood vessels in the extremities.

Product Status and Availability

Sonic CT is undergoing limited trials at the Hillcrest Center for Women's Health near San Diego. The clinical effort is being overseen by Dr. Linda Olson, a professor at the University of California at San Diego.

Doppler CT remains in the research and development phase.

Fiber Optics and Lasers

Endoscopy and laparoscopy caused a minor revolution in patient care, turning many inpatients into outpatients and reducing morbidity associated with more invasive procedures. Fiber-optic techniques have enabled remarkable strides in the visualization of internal anatomy. The nasal sinuses, esophagus, lung, colon, and bladder can all be examined and biopsied endoscopically, with far fewer complications than with exploratory surgery. Laparoscopy, a more invasive version of endoscopy, has facilitated diagnosis and treatment of gynecological disorders, liver dysfunction, and abdominal disorders.

Strengths

In addition to providing a window into the body's functions, fiber-optic technology has also provided the means to deliver laser light to tissues inside and on the surface of the body. Lasers are being used to treat dermatologic conditions such as spider veins and portwine stain birthmarks. Some ophthalmic applications include repair of retinal tears and damage caused by diabetic retinopathy. Fiber-optical endoscopy has replaced the fluoroscope for some examinations, and can be used to deliver laser light to the bladder, lungs, uterus, and gastrointestinal tract. Clinical research is under way for laser destruction of blood clots in coronary arteries, with possible future applications in smaller cerebral arteries.

Limitations

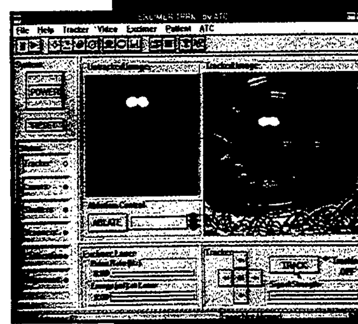
In treatment of living tissue, laser light wavelength is selected such that only certain tissues, or components of tissues, absorb the wavelength's energy. Hemoglobin, for example, absorbs strongly in the complementary visible wavelengths of about 480 to 570 nm, which is roughly yellow-green. This wavelength has already proven to be useful for destroying intra-arterial blood clots while sparing the relatively hemoglobin-free arterial wall. In other tissues, however, it is difficult to choose a wavelength that distinguishes between benign and malignant cells, since these cells have generally similar elemental features but their structures may be quite different. Determining empirical values of cell features requires databases that contain extensive cellular information; this problem is being addressed by researchers in many fields. Low-power laser light in the ultraviolet range has the potential for examining DNA, and therefore tissue ploidy (an indicator that can help identify malignancies), but these methods must also be supplemented by specific knowledge of cancer's molecular biology. For in vivo use, the known biological effects of ultraviolet (UV) radiation must also be taken into account. This concern also exists in the use of UV lasers for corneal shaping, where corneal clouding (disturbingly similar to cataract formation) has been noted as a sequela. Shortwave UV radiation is also associated with skin cancers.

LADAR Locks Onto Eye Movements

BMDO Technology Background

Autonomous Technologies (Orlando, FL) originally developed monopulse laser radar tracking techniques for military purposes. The company received three BMDO SBIR contracts to develop laser radar (LADAR) systems for missile tracking and space docking. Today, the company has extended that technology to photorefractive keratectomy (PRK), a procedure that can improve near-sightedness by modifying the shape of the cornea.

In 1993 Autonomous received private investor funding to develop its T-PRK® Alpha Unit. This unit was a direct result of a prototype LADAR eye tracker developed under a BMDO SBIR Phase II project.



▲ T-PRK® helps make laser surgery for myopia safer and more accurate.

How It Works

The surgical effectiveness of photorefractive keratectomy depends on accurate delivery of an excimer laser beam to the surface of the cornea. Tracking the continual, involuntary eye movements known as saccades improves this accuracy and reduces dependence on patient fixation of a target. Without the ability to track and compensate for this motion, the laser beam might unintentionally ablate the wrong tissue while sculpting the cornea.

Autonomous Technologies has adapted object detection and ranging technology originally developed for missile targeting and space docking systems to track irregular eye movements. This eye tracking system, or LADARVision™, is a key component of Autonomous Technologies' new medical laser product known as T-PRK®. This surgical laser device integrates a UV excimer laser to a LADAR-based tracking system. LADAR uses laser photons reflected from a specific object for tracking or imaging.

The company hopes to receive FDA approval for the device as soon as 1997 or 1998.

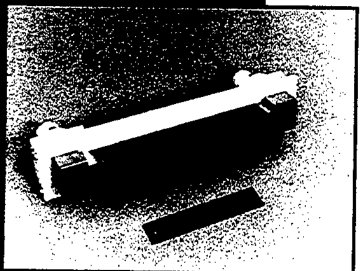
Potential Use to Medicine

T-PRK™ is a valuable tool for the ophthalmologist who specializes in refractive surgery. It reduces the risk of inaccurate ablation caused by eye movement during laser firing. Six-month post-surgical data from a trial site in Greece show good results in procedures using T-PRK®. Preliminary data indicate that no significant loss of BCVA (best corrected visual acuity) had taken place, and minimal corneal haze, a frequent side effect of PRK, was noted. Endothelial cell density, a diminution of which would indicate cellular damage, was unaffected. Uncorrected visual acuity in 68 percent of treated eyes was 20/40 or better, with 20/20 rated as "perfect" visual acuity. Taken together, these data support the efficacy of T-PRK®.

Product Status and Availability

In June 1994, Autonomous and CIBA Vision Ophthalmics, a producer of ophthalmic pharmaceuticals and a business unit of CIBA Vision, formed a strategic alliance to market T-PRK®. Autonomous began clinical trials for T-PRK® in two sites in Greece and plans to have units in place for U. S. trials by mid-1996. The company hopes to receive Food and Drug Administration approval for the device as soon as 1997 or 1998. Marketing for T-PRK® has begun in several other countries.

High-Powered Lasers Stay Cool



A two-dimensional diode array for pumping a Nd:YAG slab laser. ▲

Lasers can treat birthmarks and skin lesions that were once untreatable.

BMDO Technology Background

In 1994, Beckman Laser Institute (Irvine, CA) and Lawrence Livermore National Laboratory (LLNL; Livermore, CA) embarked on a 2-year, $1.3 million cooperative research and development agreement (CRADA) to develop laser-based medical systems. Through BMDO's Medical Free Electron Laser research in micro-optical lenses and microchannel coolers, these two groups have teamed in a CRADA to develop three laser prototype systems.

How It Works

High-power laser diodes and diode-pumped microlasers have advantages over flash-lamp-pumped solid-state lasers, but laser diodes generally have greater beam divergence, limiting the degree of focus that can be achieved. LLNL has developed a cylindrical microlens for divergence correction. The microlens focuses the radiation from each diode bar, enabling the output radiation from the diode stacks to be efficiently delivered to the end of rod lasers. The laser then operates more efficiently and can achieve higher power levels than it can without the lens. A fiber-optic pulling technique, in which the material is kept cool and viscous to retain the shape of the pre-form, can be used to manufacture thousands of the microlenses quickly and affordably.

For high-power semiconductor lasers, heat extraction from the laser-active medium is also important. The silicon microchannel cooler allows laser-diode packages to efficiently shed the large heat intensities generated at the laser-diode array with only a slight rise in temperature. These coolers are microscopic water channels buried beneath the silicon surface of the package; the channels are created using standard photolithographic techniques.

Potential Use to Medicine

The CRADA between Beckman and LLNL was established to further research in three specific areas. The first is the development of a cancer treatment called photodynamic therapy. After chemical photosensitizers are given intravenously to the patient, lasers tuned to specific wavelengths illuminate the diseased area and cause the photosensitizers to give off an oxygen radical that damages tumor cells.

Another laser system, which is still in the basic research stage, will be used in fertility treatment for both humans and animals. Lasers will drill tiny holes in the surface of eggs, increasing the chances of sperm penetrating the egg casing.

A third system will improve existing techniques for removing portwine stains (purplish birthmarks) from infants and young children. The lasers heat and destroy abnormal vessels below the skin surface, removing the discoloration after several treatments. LLNL's advances will allow physicians to adjust the duration of the laser's pulse, tailoring it to the patient. Current efforts for treatment of portwine stains center on improving energy levels of the laser pulse, and shifting the wavelength of the laser from 523 to 589 nm. A chicken allantoic membrane, which is a blood-vessel-rich embryonic membrane, is the test material.

Product Status and Availability

These research methods are under development.

Optical Biopsy Promises Early Detection

BMDO Technology Background

The City College of New York's Institute for Ultrafast Spectroscopy and Lasers (IUSL) has shown that light-induced fluorescence spectroscopy can be used to distinguish normal breast tissue from cancerous breast tissue. In research derived in part from BMDO's Medical Free Electron Laser program, investigators were able to identify malignant tissue with up to 96 percent accuracy. Many other medical facilities, including those at Harvard, Yale, MIT, and the M.D. Anderson Cancer Center at the University of Texas, are pursuing studies in this area.

How It Works

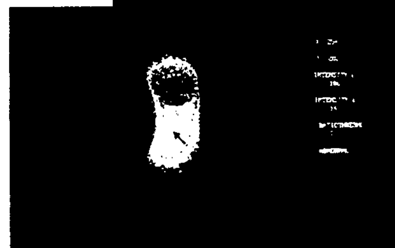
In this particular method of optical spectroscopy, the tissue under scrutiny is illuminated with a laser or a lamp light, causing the tissue to fluoresce. The characteristics of this fluorescence signature are measured to indicate chemical composition. In the studies conducted at IUSL, wavelengths from 340 to 440 nm were used to examine the collagen and elastin content of breast tissue, as well as chemical indicators of energy consumption. Consistent differences in spectroscopic signatures were seen in malignant versus benign tissue samples.

Potential Use to Medicine

Early detection of precancerous or cancerous changes in human tissues is crucial to effective treatment of malignancies. Optical methods can help to eliminate or reduce the need for surgical biopsy and allow treatment to take place before a cancer is well-established or spreading. Optical biopsy could become an adjunct to mammography for breast cancer screening, helping to further distinguish suspicious or inconclusive images.

Product Status and Availability

These methods are in development.



▲ A fluorescence image of abnormal breast tissue, using a breadboard version of the Spectral Mapping Optical Biopsy Cancer Diagnosis Unit.

Fluorescence signatures of tissues can yield important information about living cells.

Fast Lasers Take Molecular Snapshots

A living heart muscle as imaged with a two-photon scanning laser microscope, using a Clark-MXR, femtosecond laser.

BMDO Technology Background

Clark-MXR (Dexter, MI) developed compact, femtosecond laser sources under the auspices of ballistic missile defense, but found a number of biological and medical applications for this device. Very short laser pulses can help to determine, for instance, the depth of a surgical incision.

A Phase I BMDO SBIR was awarded to, and completed by, Medox Research, Inc. in 1992 before it formed a joint venture with an instrumentation firm. The joint company is working on the Phase II SBIR. Michigan's State Research Fund and the Michigan Department of Commerce also funded this program.

How It Works

Clark-MXR is developing small ultrafast optical sources that are more practical for applications beyond the laboratory. The company is using laser diodes—small and relatively inexpensive lasers used in laser printers—to pump femtosecond optical sources. Clark-MXR's latest pump source is 300 times smaller and 60 times lighter than traditional ultrafast optical sources. A process called self-modelocking is used to achieve this smaller and less complex design.

Traditional femtosecond optical sources also require skilled machine operators to generate short pulses, because these sources drift out of physical alignment and stop producing short pulses when left alone. As a by-product of their research on compact femtosecond optical sources, Clark-MXR developed a computer-controlled alignment system for femtosecond lasers.

Traditional optical sources have been too large for commercial applications, but these compact femtosecond optical sources open the door to many biomedical, robotic, defense, and sensor applications.

Very short laser pulses can used for imagery and surgery.

Potential Use to Medicine

According to Clark-MXR's Phillipe Bado, a femtosecond is an interval in which time is essentially frozen. In this interval, he asserts, DNA strands do not vibrate, and even the Federal deficit refrains from increase. This "flash" picture of physical phenomena helps us to understand the many steps that make up any dynamic process. Using femtosecond optical sources with ultrafast detectors, objects can be imaged directly through highly scattering media such as tissues of the human body. Instead of high energy lightwaves, which can warm the sample and cause photodamage, the femtosecond laser imaging system uses "peak power" to substitute for high energy wavelengths. These sources may be used, for example, to detect subcutaneous tumors or fluids in the lungs.

Lasers can also be used for surgery. The shorter pulse duration of femtosecond laser sources provides a clean cut, wound coagulation, and a simple way to assess the depth of the incision. Using femtosecond pulses and ultrafast detectors, the incision depth can be measured with a resolution of a few tenths of a micron. Incision depth can be measured in real time while the surgeon is operating.

The peak intensity of lasers can be used to measure molecular concentration and motion in cells. Macromolecular movement on and in living cells provides information on how cellular functions are carried out. For example, the diffusion of the low-density lipoprotein molecule on the cell surface helps regulate serum cholesterol, a health parameter that is routinely measured in cardiovascular assessment.

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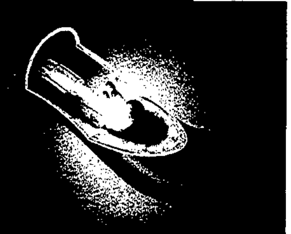
Three-dimensional models of the specimen can be constructed by treating the specimen with a fluorophore—a substance that will fluoresce when appropriately excited—and applying laser beams through a complex process. Previously, this method had distorted images and induced photodamage (or photobleaching) along its path through the specimen, resulting in areas of washout within the image. A more refined two-photon excitation process, which requires ultrafast optical sources, produces ultraclear images with less work, and reduces cellular damage. Large laser sources would be impractical, but compact laser sources developed under the BMDO program will make two-photon confocal scanning an immediate commercial reality. At the basic research level, two-photon confocal microscopy has already shed considerable insight on molecular structures.

Product Status and Availability

Clark-MXR is collaborating with Dr. Ron Kurtz of the Kellogg Eye Center of the University of Michigan (Ann Arbor, MI) to evaluate the quality of laser incisions on biological tissues. The company is also working with Picometrix, Inc. (Ann Arbor, MI) on evaluating incision depths for surgical applications.

Lasers Safely Target Blood Clots



A laser safely eliminates a blood clot in this schematic drawing.

Laser thrombolysis may become a safe alternative or adjunct therapy for coronary artery blockage.

BMDO Technology Background

Unique expertise and resources residing at Los Alamos National Laboratory (LANL; Los Alamos, NM) allow the laboratory to support Theater Missile Defense (TMD) studies for BMDO. The technical capabilities involved include laser-matter coupling, remote laser sensing, and the experimental and computational study of the dynamic-hydrodynamic response of materials to pulsed heating and projectile impacts. These studies are facilitating the development of a clot-removal technique called laser thrombolysis through the work of Dr. Kenton Gregory at Providence St. Vincent's Hospital (Portland, OR). Palomar Medical Technologies (Bedford, MA) is helping to provide instrumentation.

How It Works

Laser thrombolysis, performed with standard cardiac catheterization techniques, may be a great improvement over present treatments. Using visible laser light in very short pulses, a fiber optic, coupled to the laser, is inserted into the catheter and placed 20 cm proximal to the tip of the catheter. A fluid (radio-opaque dye) is passed through the catheter and transmits the light from the end of the optical fiber through the end of the catheter to the clot, where it vaporizes the clot without damaging the arterial wall. This fluid-core optical catheter allows delivery of the laser light while washing away ambient blood. Because radio-opaque dye is used, this process can be viewed in real time via fluoroscopy.

Potential Use to Medicine

Currently, there are several ways to treat a blocked coronary artery, which can cause angina (pain) and infarction (heart attack). In balloon angioplasty, a catheter is inserted through an artery near the hip and threaded up into the major cardiac vessels. Once inserted, a balloon at the tip of the catheter is inflated, and the clot is displaced. Another treatment is enzymatic: a tissue-derived drug such as tissue plasminogen activator, (tPA), or a bacterial product called streptokinase is used to dissolve the clot. A third treatment, coronary artery bypass surgery, is performed when the previous treatments fail. All treatments have potentially significant drawbacks, and blockage frequently recurs within a year.

In laser thrombolysis, researchers hypothesize that the hemoglobin of the clot absorbs the laser light much more efficiently than the arterial wall, which means that the clot can be heated and dissolved without damaging adjacent structures. The platelets in the clot are also eliminated, which reduces the chance of a new clot forming from the released debris. Avoiding damage to the arterial wall is also important to the prevention of perforations (holes), dissection (splitting), or restenosis (renarrowing) of the artery. Since the radio-opaque dye used in these procedures is also transparent to the laser beam's wavelength, the laser method is compatible with existing catheterization protocols.

Product Status and Availability

Once developed, laser thrombolysis has the potential to treat over 100,000 patients per year. The method must undergo further refinement, and get Food and Drug Administration (FDA) approval for widespread clinical use before it can become commercially viable; however Palomar Medical Technologies is a subsidiary of a major venture capital corporation and would be suited to carry out commercialization. At present, FDA-sponsored testing involves 60 heart attack patients, over a period of 1 year, in four U.S. centers; Providence St. Vincent's Hospital (Portland, OR),

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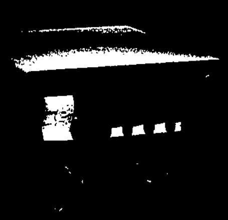
Washington Hospital Center (Washington, D.C.), Scripps Clinic (La Jolla, CA), and Methodist Hospital (Lubbock, TX). A recent trial used a laser wavelength of 585 nm for optimal hemoglobin absorption, and light was delivered by a "flowing liquid core" catheter that allows transmission of the beam to the clot while washing away ambient blood.

A CRADA funded by the Department of Energy was initiated in early 1995 and is expected to run for 3 years. Studies involving in vitro gels that simulate clots and surgery in pigs are being conducted to define the parameters of the method and to improve safety and efficacy. LANL is lending its expertise in laser technology, computational analysis, and hydrodynamic behavior. Palomar Medical Technologies is providing lasers and catheters, and clinical and laboratory work are being conducted at the Oregon Medical Laser Center.

Gas Analysis Aids Anesthetists



Ohmeda's Rascal II anesthetic gas analyzer makes surgery safer.

BMDO Technology Background

Supported in part by BMDO's Medical Free Electron Laser program, a group of researchers from the University of Utah built a prototype Raman gas analyzer for medical gas applications. Their company was subsequently bought by Ohmeda (Louisville, CO). One of their more notable products is the Rascal II anesthetic monitor, 1,500 of which are now in U.S. operating rooms. The device is a Raman spectroscopic gas analyzer, and it enables the anesthetist to monitor physiologic gases such as oxygen and carbon dioxide, as well as anesthetic gases, in real time. The Rascal II won an R & D 100 award in 1993.

How It Works

Based on a helium-neon laser, the Rascal II directs its beam into a sampling chamber and excites the molecules of the sampled gas, sending its electrons into a higher energy level. When the electrons fall back to a lower energy level, they emit scattered light at a longer wavelength than that of the original beam. The change in wavelength is unique to the chemical composition of the gas, and this change can be measured to identify the compound.

Potential Use to Medicine

The Rascal II's ability to monitor gases in real time is of inestimable value to the anesthetist, who can observe changes in the patient's reaction to anesthesia, such as respiratory distress, and respond accordingly. Complications can develop quickly with the use of general anesthesia, so early detection of problems is very important.

Product Status and Availability

The Rascal II is an established device, widely distributed in the United States. Ohmeda is currently designing the next generation of monitors, which will have capabilities beyond those of the current model.

Anesthetic gas analyzers are now an integral part of the operating room.

Photodynamic Therapy Shows Selective Action

BMDO Technology Background

As a result of work performed at the Baylor Research Institute (Dallas, TX), partially funded by BMDO's Medical Free Electron Laser program, a number of photochemicals were studied, one of which was licensed to QLT Phototherapeutics, Inc. (Vancouver, British Columbia). This company has gone on to make excellent progress, resulting in some Food and Drug Administration-approved treatments for specific cancers, as well as significant clinical and preclinical trials for both benign and malignant conditions.

▲ A flexible fiber-optic coil.

How It Works

Photosensitive chemicals used in photodynamic therapy (PDT) are generally ring-structured, dye-related compounds that react with light to produce free radicals such as singlet oxygen. Well-known to students of the immune system, singlet oxygen is naturally generated by enzymes to mediate the inflammatory response to disease. This radical causes local cell damage, thereby destroying infectious agents and diseased cells. PDT reproduces this phenomenon with exogenous compounds. In QLT's protocols, the photochemicals are injected intravenously, and the affected organ is exposed to low-power laser light of a wavelength specific to the chosen photochemical. Patients thus treated must avoid exposure to the sun for 4 to 6 weeks.

Potential Use to Medicine

In treating disease, chemical agents often lack specificity. A compound as simple as aspirin, while an effective pain reliever, can also cause hemorrhage, and even ringing in the ears. Experience with photosensitive chemicals has empirically shown that diseased tissue takes up these chemicals more readily than healthy tissue. Moreover, the cell-killing activity is largely confined to the diseased tissue. This result is a great improvement over current chemotherapeutic agents, which are essentially cell poisons that don't discriminate between normal and abnormal tissues.

PDT is becoming an increasingly acceptable procedure for treating some malignancies.

Product Status and Availability

QLT is making rapid progress in testing PDT. QLT recently received FDA preapproval for Photofrin. Its generic names are dihematoporphyrin ether or sterile porfimer sodium. Photofrin has been approved in Canada for bladder cancer treatment and in Canada, the Netherlands, and Japan for lung and esophageal cancer.

QLT is testing a second-generation benzoporphyrin derivative (BPD) in phase II clinical trials on psoriasis and basal cell carcinoma in the United States and Canada. In conjunction with CIBA-Geigy, QLT is also conducting a phase I clinical trial of BPD for macular degeneration, a common age-related eye disease, in the United States and Europe. BPD is also seen as a possible treatment for breast cancer recurrences on surgical incisions. Preclinical work is being conducted with BPD for preventing restenosis after balloon angioplasty and, based on BPD's observed effects on T-cell activation, for rheumatoid arthritis.

CIBA-Geigy has licensed zinc pthalocyanine to QLT. Tests with this compound, which are in the preclinical stage, suggest that it is a candidate for topical treatments in dermatology, for conditions such as psoriasis, or malignancies such as basal cell carcinoma.

PET, SPECT, and Particle Beam Therapies

Positron emission tomography (PET) is a minimally invasive imaging procedure that uses radioactively tagged metabolites to image organs and to illustrate some metabolic pathways. Blood flow in the brain, for instance, can be viewed by injecting fluorine-tagged glucose into the bloodstream. The radioactive fluorine emits positrons, which collide with electrons, to produce two gamma rays that travel in opposite directions. The gamma rays strike a scintillator, and an image of the organ is formed.

Strengths

As the brain uses about 60 percent of the blood's glucose content, the tagged compound quickly accumulates in cerebral tissues. By issuing cognitive tasks to the subject under scrutiny, one can see which parts of the brain are active during reading, counting, speaking, and so on. A fast-growing tumor, with its avid appetite for glucose, can also be imaged. Areas affected by occlusive stroke can be identified by their failure to take up the isotope.

SPECT, or single photon emission computed tomography, is a cousin of PET. It also uses radiopharmaceuticals, but it uses tomographic techniques to image their distribution. Thus, as in computerized axial tomography scanning, slices of the anatomy can be viewed, eliminating interference from overlying tissues.

Particle accelerators are used to produce isotopes of carbon, oxygen, nitrogen, and fluorine for PET and SPECT. Accelerators can also be used in directed energy therapies, such as proton delivery to deep-seated tumors. This type of energy delivery has advantages over conventional radiation therapy. The beam of ions can be controlled and focused by magnetic fields, delivering maximum destruction to the tumor and helping to spare normal cells. By contrast, X-ray therapy suffers from scatter and attenuation as radiation travels through healthy tissue, and can cause undesirable and sometimes grave side effects.

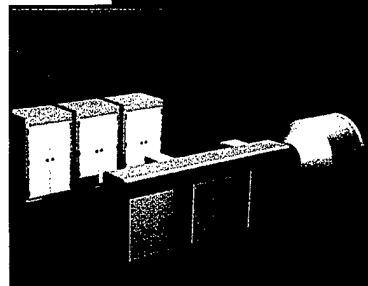
Limitations

Both PET and SPECT expose the individual to limited amounts of ionizing radiation.

Affordable Particle Beam Therapies

BMDO Technology Background

AccSys Technology, Inc. (Pleasanton, CA) developed a superconducting radiofrequency quadrupole linear accelerator (RFQ linac) in cooperation with Argonne National Laboratory (ANL), using funding from BMDO and the Department of Energy. Developed to improve BMDO's neutral particle beam systems, the compact RFQ linac can replace large, prohibitively expensive cyclotrons for use in radioisotope production.



▲ Conceptual drawing of AccSys' Pulsar™ apparatus.

How It Works

Using powerful electromagnetic fields, an RFQ linac hastens charged particles along a pathway until they reach a speed that is useful in such high-energy tasks as bombarding elements to produce unstable isotopes or delivering high-speed protons to a deep-seated tumor. AccSys and ANL participated in a cooperative research and development agreement (CRADA) to employ superconducting materials in a prototype device, cooled to 4.6 K with liquid helium. Positively or negatively charged hydrogen molecules can be accelerated and delivered to cancer cells. Radioisotopes such as oxygen-15 and fluorine-18 can also be produced.

Potential Use to Medicine

Accelerated ions such as protons can be delivered to biological tissues with less collateral damage than that associated with X-ray exposure. Superior beam delivery is another advantage of particle accelerators, with minimal attenuation of the directed energy. Radioisotopes for such tracer pharmaceuticals as fluorinated glucose (fluorine-18 coupled to glucose), which in turn can be used to illustrate metabolic processes in PET, can also be manufactured with RFQ linacs.

High-energy beams can target tumors with little collateral damage.

Product Status and Availability

An AccSys room-temperature proton linac, also based on BMDO-funded development, was installed at Loma Linda University Proton Cancer Treatment Center (Loma Linda, CA) in 1990. Loma Linda is treating 50 to 60 cancer patients a day with the directed energy therapy. Up to four patients can be treated simultaneously in the center's $80 million facility.

AccSys' Pulsar™ room-temperature product series offers state-of-the-art design, compactness, multiple-beam configurations for simultaneous delivery to multiple targets, and an upgradeable system. The system is affordable and self-shielding, and lends itself to widespread use in clinical settings. It can deliver both protons and negatively charged hydrogen ions.

The Pulsar™ can also be used to produce oxygen-15 (water, diatomic oxygen, and carbon monoxide), nitrogen-13 (in the form of ammonia), carbon-11 (carbon dioxide or monoxide), and fluorine-18 (fluorine ion or fluorine-tagged glucose). AccSys is working under a joint agreement with the PET chemistry group at Brookhaven National Laboratory to further develop appropriate targets for the Pulsar™.

Sensitive Photodiodes Reduce Cost, Increase Resolution

API's photodiode technologies can improve the resolution and sensitivity of medical images.

BMDO Technology Background

Advanced Photonix, Inc. (API; Camarillo, CA) has developed large-area silicon avalanche photodiodes that are among the first solid-state devices to provide a high-gain, low-noise, large-area replacement for photomultiplier tubes (PMTs) used in a selected range of light detection applications. Avalanche photodiodes bring the same qualities of ruggedness, small size, and low cost to light detection and imaging that other semiconductors have brought to the rest of the world of electronics.

Early research on API's avalanche photodiodes, supported in part by a 1987 BMDO SBIR contract, was conducted at Xsirius Scientific, Inc. (Los Angeles, CA). In 1988, Xsirius formed API to commercialize this technology. In 1992, API received another BMDO SBIR contract to develop single-chip photodetector arrays; these arrays are made by subdividing large-area avalanche photodiodes into an array of isolated pixels.

How It Works

API's photodiode arrays fill the gap between large-format focal plane arrays, which have the pixels to resolve images spatially but lack the sensitivity needed for many applications, and PMTs, which are very sensitive but lack the pixels needed for spatial resolution. API's arrays also make detectors more sensitive over longer distances, permit fabrication of multichannel receivers with a larger field of view, and give detectors a higher dynamic range.

API's avalanche photodiodes can detect light in all visible wavelengths and in parts of the ultraviolet and infrared spectra. They can also directly detect X-rays and charged particles, and can detect gamma rays when they are coupled to scintillating crystals or fibers.

Avalanche photodiodes can directly detect X-rays and provide larger fields of view for medical imaging.

Potential Use to Medicine

The capabilities of API's photodiode arrays will be important in medical imaging applications where sensitivity and resolution (both energy and time) are important. Photodiode arrays can indirectly sense gamma emission in PET, gamma camera, and SPECT applications. API is currently pursuing PET imaging applications in a contract with CTI PET Systems, Inc. (Knoxville, TN).

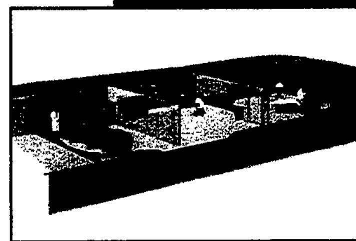
Product Status and Availability

In the CTI contract, API is building photodiode arrays for CTI to incorporate into its PET scanners. While API has already built some prototype arrays for this contract, the company is working to improve the detectors' reliability through enhancements in wafer processing. API would like to increase the current avalanche photodiodes' reliable lifetimes of about 1 year to at least 5 years. If successful, CTI PET Systems will have the first option to license the technology for this application.

Smaller, Lighter Accelerators Boost PET Availability

BMDO Technology Background

With the help of a proof-of-principle contract for the BMDO SBIR program (plus follow-on funding from the Department of Energy and the U.S. Army Research Laboratory), North Star Research Corporation (Albuquerque, NM) has developed a compact, direct current accelerator that employs a series of nested stages, each one totally isolated from the others, to accelerate particle beams of protons, electrons, neutrons, and heavy ions. Because it employs nested stages, this accelerator, known as the Nested High Voltage Generator (NHVG™), is smaller, lighter, more reliable, and less expensive than traditional direct current accelerators.



▲ PracSys implements North Star's accelerator technology in a complete PET system.

How It Works

Nested stages are based on the principle of the Faraday cage, which allows the construction of a series of concentric shells one inside the other, each one electrically isolated from the others. In the NHVG™, electronics internal to each shell maintain a preset voltage difference from one stage to the next.

The electrical isolation provided by this scheme greatly reduces the accelerator's size, weight, and cost. In addition, the nested stages are designed so that an electrical breakdown in one stage does not stress the others. Therefore, if a few stages fail, the accelerator can continue operation with no risk of further damage to the machine. Failed stages can then be replaced in a single day, greatly reducing the accelerator's maintenance downtime.

The NHVG™ can operate both in a tandem mode and a single-ended electrostatic mode. Tandem-mode operation provides higher kinetic energy levels with less power output; however, it can only accelerate certain particles, such as the proton or deuteron. Single-ended accelerators, though less efficient, can accelerate any particle.

Compact accelerators are replacing cyclotrons for the generation of radiopharmaceuticals.

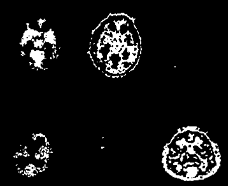
Potential Use to Medicine

A tandem-mode NHVG™ can replace larger, more expensive cyclotrons used to produce radiopharmaceuticals needed for PET imaging. Direct-beam radiotherapy is another possible medical application.

Product Status and Availability

Accelerators for medical use are licensed to PracSys Corporation (Woburn, MA) for distribution.

Tandem Cascade Accelerator Finds Multiple Applications



PET images show chemical activity in the brain.

BMDO Technology Background

Science Research Laboratory (SRL; Somerville, MA) has developed compact electrostatic accelerator technology that uses three advanced components developed under BMDO SBIR contracts: an all-solid-state high-voltage power supply, a high-current negative ion source, and a user-friendly automated control system. These innovations allow SRL's cascade accelerators to provide ion beam currents up to 10 times higher than conventional cyclotrons at one-half the size, one-fifth the weight, and one-half the cost.

How It Works

Electrostatic accelerators use strong electric fields to accelerate charged particles through an evacuated tube; the stronger the voltage difference between the ends of the tube, the greater the final acceleration. However, rather than producing one large voltage drop at each end of the accelerator, these accelerators have a cascading series of electrodes that distribute the electric field more evenly throughout the accelerator and permit more control over the beam. SRL's cascade accelerators can produce beams of protons, deuterons, and electrons with an energy of up to 6 MeV.

SRL currently operates three engineering prototypes of the cascade accelerator: a 600 keV deuteron accelerator, a 600 keV electron accelerator, and a 3.7 MeV proton and deuteron tandem cascade accelerator (TCA). The TCA achieves higher energies through a design in which a negatively charged hydrogen ion is stripped of its electrons halfway through the accelerator (making it a positively charged proton). Because the positive ions will accelerate to double the speed with an easily reversed voltage difference, this scheme transmits maximum kinetic energy with minimum power output.

SRL's accelerators are compact and cost-effective.

Potential Use to Medicine

The TCA was designed to produce radioisotopes for PET. To be used for this application, accelerators must produce the four most common radioisotopes—fluorine-18, nitrogen-13, oxygen-15, and carbon-11. With the help of the BMDO miniaturized PET accelerator program, SRL has developed the targetry and the robotic radioisotope synthesis system needed to adapt the TCA to the task of radiopharmaceutical production.

Other medical applications for SRL's accelerator technology include boron neutron capture therapy for treating deep-seated brain tumors; dual-energy, digital subtraction angioplasty for noninvasive imaging of the coronary arteries; and gamma resonance imaging for nutritional assessment. Gamma resonance imaging can image certain elements, such as nitrogen or calcium, that selectively absorb radiation produced when an ion beam is directed onto a target material.

Product Status and Availability

In May 1993 the TCA-based radioisotope delivery system was installed in the new Neuroimaging Research Center at the Washington University School of Medicine (St. Louis, MO), one of the foremost PET imaging centers in the world. Since then, the TCA has routinely generated three different oxygen-15 radiopharmaceuticals for the center, and demonstrated the ability to produce fluorine-18 and nitrogen-13. Reliability of the TCA system has been excellent, producing as many as 20 batches of radiopharmaceuticals in a day (limited only by operators' time, not the machine) and operating with virtually no maintenance downtime.

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The TCA is now on schedule to become the major source of radiopharmaceuticals for the Neuro-PET program at Washington University. A scanner will be installed directly above the TCA and delivery lines of the oxygen-15 system have been installed from the TCA to the PET room. In addition, human-use approval is currently being sought for TCA radiopharmaceuticals.

SRL also has had discussions with more than 15 organizations interested in commercializing PET imaging systems and is now receiving inquiries from potential customers for the TCA-based PET systems.

Linear Accelerators Replace Cyclotrons

An inside view of an RFQ linac from SAIC.

RFQ linacs can help to make PET systems more affordable.

BMDO Technology Background

Science Applications International Corporation (SAIC; San Diego, CA) is developing a PET Tracer Production System that will replace cyclotron accelerators, which weigh a minimum of 20 tons. SAIC's system, which is about 17 feet long and weighs about 2 tons, consists of three RFQ linacs, the targets in which the radioisotope materials are created, and the chemical processing systems that synthesize the final radiopharmaceuticals required for PET. SAIC is developing the RFQ linac and the University of Washington Medical Center, a subcontractor, is developing the targets and chemical processing systems.

SAIC began developing this system with funding from BMDO's Miniaturized PET Accelerator Program, which aimed to transfer new accelerator developments resulting from BMDO programs to the medical arena. SAIC was awarded this competitive contract because its approach had a high content of ballistic missile defense technology and offered many advantageous innovations. SAIC has continued development of the accelerator on its own since the program terminated in 1992.

How It Works

The heart of this PET radioisotope production system is the RFQ linac, which uses powerful electromagnetic fields to accelerate and bunch charged particles. Particles are accelerated into a target material and the high energy of this collision initiates a nuclear reaction that produces the radioisotopes needed for PET imaging.

Potential Use to Medicine

PET allows doctors to visualize metabolic processes in organs such as the brain and heart. Linacs have largely replaced cyclotrons in the production of radioisotopes used for PET. As a result, cost and space requirements have come down, allowing on-site facilities to be installed at hospitals and clinics.

Product Status and Availability

In 1994, SAIC formed a development partnership with the Fermi National Accelerator Laboratory (Batavia, IL), the Biomedical Research Foundation (Shreveport, LA), and the University of Washington. Under this partnership, which is being funded by the Department of Energy, SAIC will test its PET Tracer Production System at the Biomedical Research Foundation, one of the best clinical PET facilities in the world.

Highly Efficient Scintillating Fibers

BMDO Technology Background

Researchers at the University of Texas at Dallas (Richardson, TX) are using plastic scintillating fibers and position-sensitive photomultipliers to increase the efficiency of gamma ray detectors used in PET and SPECT imaging. The scintillators developed at UT-Dallas are made of polystyrene fibers that increase detector resolution and efficiency, resulting in detectors with excellent spatial (less than 1 mm) and time (less than 10 nanoseconds) resolution. UT-Dallas and the University of California at Los Angeles originally developed the scintillation fiber and position-sensitive photomultiplier technique as part of a BMDO project to build a space-based gamma ray telescope.

▲ PET image of an animal brain, using copper-64.

How It Works

This system works by converting incident gamma rays into visible light. When the gamma ray photons hit the scintillating fibers, the fibers emit electrons through Compton scattering or the photoelectric effect. As these electrons pass through the scintillating fiber, atoms are excited to a higher energy state. When the atoms return to the ground state, they emit light that is detected by position-sensitive photomultipliers. The signal from these photomultipliers can then produce a digital image of the original gamma ray emission.

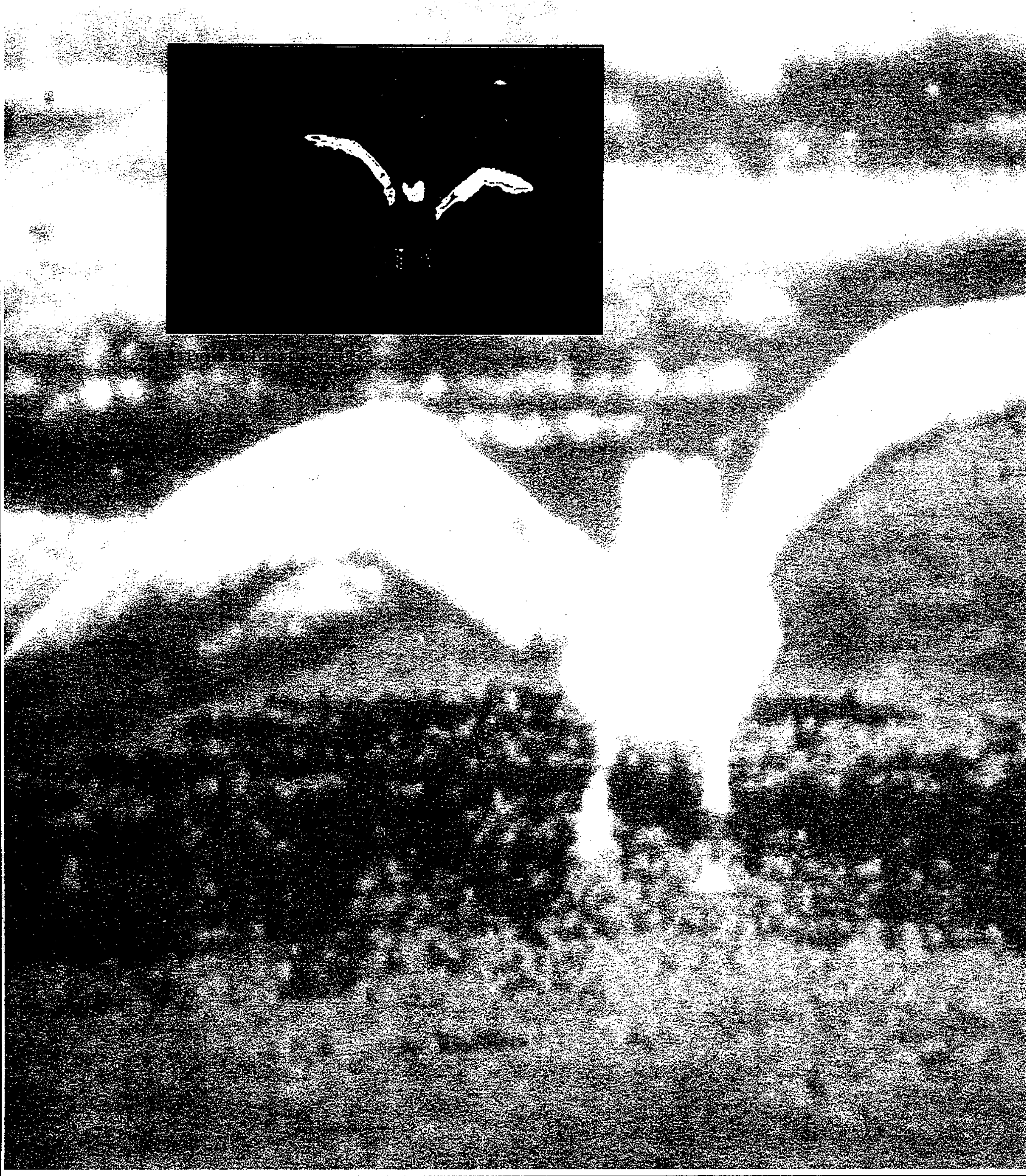
UT-Dallas technology can sharpen PET and SPECT images.

Potential Use to Medicine

UT-Dallas is now working with the University of Texas Southwestern Medical Center at Dallas to apply its gamma ray detector to SPECT and PET imaging. In both processes, a radioactive isotope is administered to a patient so that the isotope accumulates in the organ to be imaged. The isotope emits gamma radiation or, in the case of PET, positrons that produce gamma rays. The scintillators developed at UT-Dallas can increase the spatial resolution of SPECT and PET imaging about tenfold, depending on the fiber size. This increase results in sharper PET and SPECT images. Improved time resolution also will minimize background noise and accidental readings. The group also plans to use the detector technique in miniaturized endoscopic probes or imagers.

Product Status and Availability

The University of Texas system, along with some venture capital investors, has formed a spinoff company named Epikon, Inc. to further develop and commercialize this technology. A commercial prototype SPECT/PET camera based on this technology should be ready in less than 2 years. In the meantime, research continues to improve on the scintillating detector concepts and photosensor devices.



Emerging Technologies

This section presents technologies that are waiting in the wings of medicine. Fueled by new materials, streamlined software, and many years of research, techniques such as infrared sensing have gone from detecting the heat of an armored vehicle's engine to reading the glucose concentration in the bloodstream. The scatter and reflection of visible light have also been subject to rigorous interpretation, and they can now begin to tell us something about life processes without altering, surgically interrupting, or ending the process of life.

Computer-aided diagnosis has been a matter of divisive speculation in the past, but the real ability of computer and physician to interact is already being demonstrated all over the United States. Fast computing times and new algorithms can lighten the enormous data burden that now accompanies even routine examinations. Chaos theory has yielded insight into physiological phenomena such as circadian rhythm and the surprisingly nonregular rhythm of the normal heart. While these phenomena may seem erratic, discernible patterns can be elucidated by expert systems, electronic neural nets, and parallel processing. These patterns can be turned into clinically useful information.

Noninvasive IR Sensing

As any science fiction buff knows, the future is filled with optical meters that can read vital signs with one sweep of a detector and determine blood chemistries without a hypodermic. In fact, some of these capabilities already exist. Spectroscopic methods, coupled with powerful computing techniques, make it possible to disentangle optical signatures that give clues to the composition of a material, including blood and the cellular matrix.

Strengths
The immediate benefits of noninvasive blood tests include elimination of pain and a reduction in the generation of hazardous biomaterial. The latter benefit is of real concern to health care personnel, who are exposed to innumerable pathogens in the course of their work. Certain time-consuming laboratory tests can be done away with altogether, and readings can be instantaneous. Infrared (IR) sensing also has promising applications in cancer detection and biopsy, and has the potential to replace surgical sampling of tissues in some cases.

Limitations
IR has limited utility for the study of biological tissues, and is dependent on how a tissue transmits, absorbs, or reflects the range of IR wavelengths. While IR would be ideal for assessing the relative temperatures of the body, thermography has not yet proven to be an informative diagnostic tool.

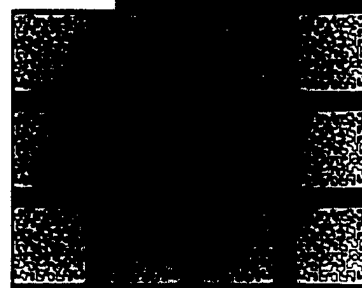
Near-IR for Noninvasive Diagnostics

BMDO Technology Background

Advanced Device Technology, Inc. (ADT; Nashua, NH) is developing IR sensors that can be used in medical applications, and readout devices that can improve image displays. Noninvasive diagnostics, particularly through IR or near-IR spectroscopy, is a clear application for ADT's sensor technology. BMDO funded multispectral focal plane array technology through Phase I and II SBIR contracts with ADT, for such military applications as target discrimination, clutter rejection, and surveillance. The program was also supported by the Office of Naval Research (ONR).

How It Works

The company's mercury cadmium telluride material is integral to its sensor technology. This sensor is a colocated dual band sensor, which means that a single sensor element, or pixel, can detect long-wave (8– 12 micron) and medium-wave (3– 5 micron) band signals simultaneously. The company is also developing monolithic gallium arsenide (GaAs)/quantum well infrared photodetector (QWIP) material in focal plane arrays. In these arrays, the readout or multiplexer (MUX) circuits are fabricated on GaAs and the detector array is fabricated on QWIP, which is grown directly on the GaAs MUX circuits. This approach allows monolithic metal interconnection between the array and the MUX, thereby providing faster readout rates. This work is supported by the ONR and is done in collaboration with the Massachusetts Institute of Technology.



Credit: Jet Propulsion Laboratory

▲ Random reflectors on pixels of QWIP focal plane array.

Potential Use to Medicine

Noninvasive IR sensing has already proven useful for detecting blood constituents such as glucose, and for determining partial pressures of blood gases, such as oxygen and carbon dioxide. Blood alcohol concentrations also can be detected with this technology.

ADT is working with Dartmouth Medical College to develop near-IR medical imaging.

Product Status and Availability

ADT is currently involved in a cooperative research effort with Dartmouth Medical College to develop a near-IR technique for medical imaging. ADT has also formed joint ventures with two companies to produce imaging systems and spectrometers. One company in the venture designs and develops readout integrated circuits, and the other develops optical components.

Tunable Filters for Industry and Medicine

Brimrose's AOTF-based spectrometer.

AOTFs can be used to noninvasively sense blood levels of calcium, glucose, and oxygen.

BMDO Technology Background

Through research originally sponsored by the BMDO SBIR program, Brimrose Corporation of America (Baltimore, MD) developed a family of acousto-optic devices that can modify laser beams in three different ways: amplitude modulation, beam deflection, and frequency shifting. In addition, acousto-optic tunable filters (AOTFs) can be used to spectrally separate and filter incoherent broadband light.

How It Works

Acousto-optic devices control laser beam phase, amplitude, frequency, and angular direction by using ultrasound to alter the refractive index of an optical medium. Progress in acousto-optics has been stimulated by new fabrication methods for acousto-optic crystals and the piezoelectric transducers used to convert electrical energy to acoustical energy.

Potential Use to Medicine

The AOTF-based spectrometer has been demonstrated to read changes in the body's calcium levels. Determination of blood calcium level can assist in the diagnosis of many diseases, such as parathyroid malfunction or metastatic cancers in bone. Anesthetists have used the spectrometer to monitor gas composition and blood oxygen levels during surgery. An AOTF-based noninvasive sensor can also measure blood glucose levels using near-IR light, making it suitable for diabetic testing.

Product Status and Availability

Brimrose has developed an AOTF-based spectrometer that could be used for online quality control and analysis in the pharmaceutical, petrochemical, polymer, agricultural, environmental monitoring, and food and beverage industries. The AOTF also can be implemented in a microscope or telescope for visible, infrared, or Raman spectral imaging in scientific and medical applications.

Spectroscopic Signatures Give Clues to Cell Status

BMDO Technology Background

In 1992, Ciencia, Inc. (East Hartford, CT) was awarded a BMDO SBIR Phase I contract to develop a dynamically adjustable amorphous material-based acousto-optic tunable filter (AOTF) to replace birefringent crystals. Ciencia has successfully parlayed this work into the commercial arena and has numerous products under development. From assessment of citrus crops to ocean surface surveys to biomedical applications, Ciencia continues to develop novel ways to decipher optical signatures.

How It Works

Acousto-optic devices use ultrasound to alter the refractive index of an optical medium, typically a crystal. Ciencia, though, has developed an AOTF based on an organic amorphous material rather than on crystals. These materials are easier and cheaper to make than conventional crystals, allow for uniformity and quality control during the manufacturing process, and permit independent control of bandpass and bandwidth. Applying mechanical stress or electric fields to the material can make Ciencia's amorphous medium birefringent. Birefringence, a type of refraction in which the speed of light through the material depends on direction as well as light frequency, allows the AOTF to separate light into different colors. Unlike an ordinary monochromator, the AOTF can be tuned electronically, so it has no moving parts. The polymeric device can also produce spectrally resolved images. AOTFs can be used in a wide range of nondestructive sensing technologies, such as determining octane ratings of gasoline and fat content in milk.

▲ Ciencia's AOTF technology used in cell fluorescence imaging.

Ciencia's technology can detect mold in citrus fruits and chlorophyll in ocean plants.

Potential Use to Medicine

Ciencia's compact, rugged Raman spectrometer can be used for in vivo tissue analysis, a method that is sought after as a means of "optical biopsy." Some malignant cells can be distinguished from their benign counterparts through unique fluorescence and Raman signatures; this difference can be detected with a high-bandwidth optical filter such as Ciencia's AOTF.

Product Status and Availability

With funding from Connecticut Innovations, Inc., Ciencia is developing filters for medical uses such as determining cell contents, and has plans for blood flow imaging. A portable spectrometer for the analysis of biological fluids, based on measurement of fluorescence lifetimes, is also being developed.

Uncooled Sensors for Thermometers

A thermographic image in infrared.

This invention won a 1993 R&D 100 award from R&D Magazine *as one of the 100 most significant innovations of the year.*

BMDO Technology Background

The BMDO Innovative Science & Technology (IS&T) program funded research at Jet Propulsion Laboratory (JPL; Pasadena, CA) on a tunneling transducer (based on scanning-tunneling microscopy) to reduce the size and increase the accuracy of a variety of sensors required for ballistic missile defense applications. The BMDO IS&T program also provided follow-on funding to develop an uncooled IR sensor and to optimize the generic transducer technology. IR sensors detect heat and therefore have potential in biological thermographic applications, such as in a thermometer, and in spectrometric applications in a gas analyzer.

How It Works

JPL's research centered on Golay cells, which are the most sensitive uncooled IR sensors. They detect the expansion of a trapped gas when it is exposed to IR radiation. Conventional Golay cells can't be miniaturized because the optical transducer that measures expansion becomes less sensitive as it gets smaller. As a result, these sensors are large, fragile, and expensive.

To make Golay cells smaller, cheaper, and more durable, JPL researchers have replaced the sensors' optical transducers with the tunneling transducer. The result is a miniature, uncooled IR radiation sensor that can be made entirely from micromachined silicon. Because of its small size and excellent stability, the sensor can be used whenever cryogenic cooling is impractical. Cooled IR sensors, such as mercury cadmium telluride, are still more sensitive than this sensor.

Potential Use to Medicine

IR sensors can be used in a variety of applications where temperature sensing and limited chemical analysis are required. Thermometers, anesthetic gas analyzers, and noninvasive blood analysis are some examples. In addition, if thermographic analysis of the human body becomes a useful clinical tool (e.g., in the detection of tumor heat), IR sensors would play an essential role in instrumentation.

Product Status and Availability

JPL researchers have produced several prototype tunneling IR sensors in a BMDO-funded project. They are currently optimizing the sensors' performance and performing life-cycle testing. Plans are also under way to further miniaturize the IR sensors to 0.5 mm pixels and develop a 20 x 1 sensor array. This invention won a 1993 R&D 100 award from *R&D Magazine* as one of the 100 most significant innovations of the year.

Painless Blood Glucose Test

BMDO Technology Background

Rio Grande Medical Technologies (RGMT; Albuquerque, NM), in collaboration with Sandia National Laboratories (Albuquerque, NM), developed a noninvasive glucose monitor that will be a great boon to the nation's diagnosed diabetic individuals. To reduce the risk of the many complications that can arise from this disease, an estimated 2.5 million patients must test their blood glucose levels up to five times a day. This testing involves painful and potentially infectious finger sticks, causes callus buildup over time, and provides an avenue for spreading blood-borne pathogens. RGMT evolved from research at the University of New Mexico School of Medicine and Sandia National Laboratories. BMDO's work in nuclear weapons stockpile assessment, as well as Theater Missile Defense, played a role in the development of the noninvasive glucose monitor, which involves in vivo near-IR spectroscopic examination of blood.

▲ Proper doses of insulin are determined by accurate blood glucose readings.

How It Works

To operate the glucose monitor, a near-IR beam is passed through the fingertip, and the spectral components of the emergent beam are measured using statistical computing and spectroscopic techniques. The level of glucose is determined by comparing the light absorbed by the glucose at a particular wavelength with the light that strikes the photodetector.

Portable, painless blood glucose monitoring is a hotly pursued field.

Potential Use to Medicine

The noninvasive sensor for blood glucose determination is an eagerly awaited development that is being pursued by more than one company. In addition to eliminating finger sticking, the monitor can provide a reading comparable to present systems (which rely on visual or digital reading of color-coded strips) and a means of quickly examining trends in blood glucose levels. Also, test strips, which cost an average of $1,500 per year per person, will not be needed.

Product Status and Availability

RGMT is working with Sandia National Laboratories within a cooperative research and development agreement (CRADA) to produce a miniaturized, robust device. A prototype monitor is now being used to collect high-precision test data from diabetic patients.

Non-laser, Visible Light Technologies

Visible light can be used to illuminate tissues and to induce cell fluorescence. Reflectance patterns from a collection of cells can also inform the viewer of certain biological parameters, such as the shape of the lens of the eye and the topography of the retina. Some wavelengths are more informative than others, and spectroscopic as well as digital computing techniques can be used to interpret their meaning. In some ways, we are just beginning to learn about the optical properties of living cells.

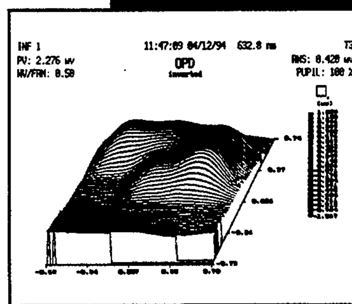
Strengths
Visible light technologies offer another noninvasive means of examination and diagnosis without the damaging energies of X-rays or ultraviolet light.

Limitations
Visible light technologies described in this section often require sophisticated methods for interpretation, and many tissue types must be sampled in order to construct a meaningful database from which to draw diagnostic information. These technologies are also restricted to accessible regions of the anatomy.

Novel Camera Detects Early Glaucoma

BMDO Technology Background

As an outgrowth of Massie Research Laboratories (MRL; San Ramon, CA) BMDO-funded adaptive optics (AO) research, the company is developing a high-resolution retinal camera, which is used to detect early changes in the retina that presage the onset of glaucoma. In this project, AO techniques are part of a retinal camera that can achieve the fine resolution necessary for discerning abnormalities inside the eye. MRL used BMDO funding to develop a very low-cost deformable mirror, which is the key to its application of AO to the retinal camera.



▲ Data sheet showing random distortions in MRL's deformable mirror.

How It Works

Deformable mirrors were originally used to eliminate atmosphere-induced distortion in optical telescopes. Used in conjunction with reference light beams, interferometers, and fast parallel processors, these mirrors help clarify images of distant stars, direct light beams in lithography, and correct laser pathways in optical communication systems.

Originally, deformable mirrors required high voltages and were exceptionally expensive. Researchers found that they could reduce voltages by placing actuators in multiple layers, but the fabrication of such multilayer systems was too expensive for broad commercial applications. MRL helped to develop a technique by which multiple actuators could be fabricated as a sheet, substantially reducing the cost and improving the reliability of the resulting device.

MRL welcomes interest from potential partners.

Potential Use to Medicine

MRL's camera will help detect the early signs of glaucoma.

Product Status and Availability

MRL's retinal camera is under development. The company welcomes interest from potential partners.

Microscope for 3-D View of Cells

A three-dimensional view of roundworm larvae.

MCR is actively seeking interested partners to commercialize its imaging technology.

BMDO Technology Background

MCR Technology Corporation (Chicago, IL) has developed and patented a visible light holographic camera under BMDO SBIR funding. The camera's ability to provide three-dimensional, high-contrast, undistorted images of hydrated biological material, is important to both medical researchers and diagnosticians. This technology can operate in the ultraviolet range with modest reconfiguration, and can be extended into the X-ray region when sources of appropriate brightness become available. This image presentation, which is uniform over the full range of spectral coverage, can be used to visualize biological matter down to the molecular level. The three-dimensional images generated from the camera can be conveniently viewed on a video display. A fluorescence lifetime multiplexed imaging system that is particularly applicable to DNA sequencing has also been designed.

How It Works

The holographic microscope collects three-dimensional image information in a single imaging exposure and can obtain undistorted optical sections. The instrument uses a relatively low light exposure and has a large effective depth of field. Because of the low exposure used, the microscope operates at visible wavelengths without photochemical bleaching, stains, or damage to the in vivo biological constituents, all drawbacks of conventional instruments.

Potential Use to Medicine

The most significant advantage of this microscope is that it can view cells without the use of destructive and substrate-altering preparations. Staining is a common method for enhancing light microscopy, and cryopreparation and treatment with toxic heavy metals are prerequisites for electron microscopy. MCR's microscope represents a significant evolutionary step in nondestructive evaluation of biological materials.

Operating at visible wavelengths, the holographic microscope can examine cell structures in three dimensions and greatly enhance the diagnosis and staging of cancers. It can also be used to image the topography of the optic disk and thus help to diagnose glaucoma and other ocular disorders.

Ultraviolet operation is ideal for examining genetic material, as DNA absorbs maximally at this wavelength. Dynamic examination of chromosome structures as they move through the cell cycle is of intrinsic interest to cellular and molecular biologists, as well as to oncologists. Detecting genetic change at the earliest possible stage could be one of the keys to diagnosing precancerous conditions or malignancies in early development.

The X-ray microscope would provide the best intrinsic resolution for viewing the molecular biology of the cell. Protein-folding, myosin-actin interaction in the muscle, gene transcription and translation, and even DNA base-pair sequences, could be examined. The dynamics of the cell membrane, which controls import and export of cell signaling molecules, could also be elucidated.

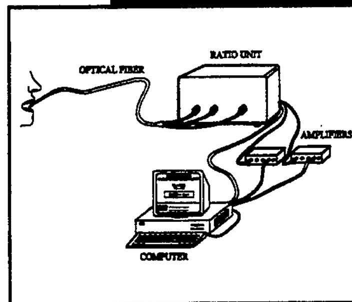
Product Status and Availability

MCR plans to license the production and marketing of the instruments to well-established companies. The company is actively seeking interested partners to commercialize this imaging technology.

Studies Advance Early Cancer Detection

BMDO Technology Background

Mediscience Technology Corporation (MTC; Cherry Hill, NJ) has used the optical spectroscopy techniques developed under the Medical Free Electron Laser program to develop an endoscope with a diagnostic tool on its end. The endoscope is currently undergoing clinical testing, and results have been promising. Other potential applications are being investigated as well.
Dr. Stimson Schantz of Memorial Sloan-Kettering (New York, NY) has been using xenon-lamp, multiple-wavelength spectroscopy to study tobacco-induced, premalignant changes in the oral mucosa, larynx, and esophagus.



Credit: Mediscience Technology Corporation (Cherry Hill, NJ)

▲ MTC's endoscope can be used to visualize precancerous tissues in Dr. Stimson Schantz's research efforts.

How It Works

In this application, non-laser light is used, in vivo, to induce fluorescence in tissues. A xenon lamp is used to deliver the light to tissues via an endoscope. Spectroscopic techniques are used to decipher unique characteristics of the fluorescence signature, which can correlate with unique features of normal or abnormal cells.

Potential Use to Medicine

Early diagnosis is the key to cancer survival. This work helps make possible the sought-after technique of noninvasive, optical biopsy, to detect changes in cells even before malignant transformation has taken place. Treatment can then be tailored to prevent the development of a cancerous condition, a much easier task than fighting an established cancer.

Optical spectroscopy may be the key to recognizing pre-cancerous conditions.

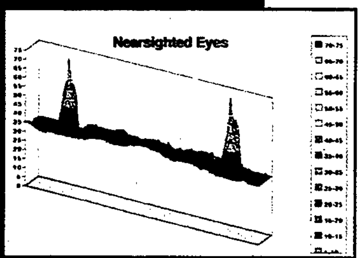
Product Status and Availability

By examining oropharyngeal tissues, Dr. Schantz has found consistent differences in the intrinsic fluorescence signatures of normal and abnormal cells, which he has determined to be based on differences in both cellular architecture and chemical composition. Dr. Schantz is currently involved in a master agreement with the National Cancer Institute to use optical spectroscopy techniques to examine the effects of retinoid (vitamin A derivative) and other therapies on premalignant lesions of the aerodigestive tract.

Regulatory Status

MTC has filed a petition with the Food and Drug Administration for an investigational device exemption (IDE) for its endoscopic device, called CD-Scan, in connection with detection of aerodigestive cancers by autofluorescence endoscopy. An IDE would enable MTC to use and sell devices for the purpose of conducting clinical trials.

Neural Networks Help Doctor's Innovation



Read-out data from Dr. Hay's ophthalmic diagnostic methods.

Neural networks can help to streamline optical diagnostic methods.

BMDO Technology Background

Nichols Research Corporation (NRC; Wakefield, MA) used BMDO funding to develop a neural network system called MLANS, or Maximum Likelihood Adaptive Neural System. Unlike expert systems that depend on hard-and-fast rules for computational decisions, neural networks can "learn" solutions from data input and speed up problem solving that depends on a large number of variables. Originally developed for BMDO space-based applications, NRC has adapted MLANS to such areas as fingerprint identification, drug traffic detection, automotive collision avoidance systems, and medical diagnostics.

Ophthalmologist Dr. S. Hutson Hay of Huntsville, AL, is making particular use of MLANS in a specialized optical device of his invention. Using a blue-light flash-lamp, Dr. Hay measures the light reflected from a patient's retina and correlates the distortion of reflected light waves with specific eye conditions. For instance, he has recorded optical signatures from patients with astigmatism, myopia (nearsightedness) and glaucoma, among other conditions. Each condition has a unique pattern of reflectance, so the device can be used for differential diagnosis of eye disorders. NRC is using MLANS algorithms to improve the processing and interpretation of these optical signatures, making for a more efficient and accurate device.

How It Works

The patient is seated in a dim room, head stabilized by a chin rest. A modified photographic flash delivers a reduced intensity light beam to the eye. A modified astronomical camera, equipped with a charge-coupled device (CCD), records the reflectance of the flash from the patient's retina. The CCD facilitates the conversion of optical signatures to digital form, and a standard 486 computer analyzes the resulting data with algorithms developed by Dr. Hay. Neural network algorithms contributed by NRC are being developed and evaluated.

Potential Use to Medicine

Noninvasive investigation of the eye offers a rapid and accurate way to diagnose both complex and relatively simple eye conditions. As in most areas of medicine, early detection of problems means a better likelihood of successful intervention.

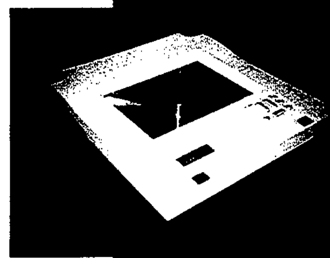
Product Status and Availability

Dr. Hay's techniques are under development.

Real Images in Real Time

BMDO Technology Background

Reveo (Hawthorne, NY) offers medicine real-time graphics and three-dimensional (3-D) imaging through its marketing arm, VRex, Inc. Some real-time applications include integrating VRex's stereoscopic cameras with microscopes used in the operating theater and displaying the output of 3-D endoscopes. The surgeon can look through his normal eyepiece to view the image produced by the microscope. In both applications, surgery can be performed using VRex's real-time 3-D display, simultaneously viewed both by those in the operating theater and at remote locations, with the use of inexpensive, passive eyewear.



▲ The world's first 3-D stereoscopic overhead projection system, which Reveo, Inc. recently introduced to the market.

How It Works

The system's μPol™ array uses polarization encoding to project two digital images simultaneously. The system uses spatially multiplexed imaging (SMI) to arrange the left and right images of a stereo pair spatially instead of by time. The system transforms incoming unpolarized light into two perpendicular polarized states, each of which passes one of the stereo pair of images. The encoded or polarized images are decoded with passive polarized glasses, and the appropriate image from the stereo pair is passed to the appropriate eye. By processing the images spatially, SMI eliminates flicker, so it can be used for video and television. In addition to producing 3-D images for all VRex display devices, SMI is able to generate 3-D hardcopy transparencies.

Potential Use to Medicine

In a 1994 demonstration of the technology at New York University School of Medicine, the VRex CAM-3000C stereo camera and VR-2000 projector were used to display and record an ablation of a metastatic tumor of the cerebellum. The CAM-3000C was placed on parallel beam ports of a Zeiss OPMD surgical microscope, allowing students, nurses, and anesthesiologists to view the surgery projected in stereo at the same time the neurosurgeon worked through the eyepieces of the microscope. A stereo videotape of the operation was available for teaching purposes afterward.

3-D imagery of human anatomy can make delicate surgery safer and help to train young doctors.

In demonstrations of stereo endoscopy with the VRex system at numerous medical conventions, surgeons have acknowledged the advantages of the 3-D capability. Compared with two-dimensional endoscopes, depth perception is restored, operating time is reduced, and movements are executed to precise depth locations. These advantages are crucial in such procedures as sinus endoscopy, where bony dehiscences of the subcranial space raise the risk of damage to the brain, optic nerve, and carotid arteries.

Product Status and Availability

Stereo endoscopes from American Surgical Technologies (McKinley patent optics), Richard Wolf, Carl Zeiss, and Applied Surgical Concepts are compatible with the VRex system. The endoscope output is multiplexed through the VRex VRMUX and can be displayed with the VR-2000 stereo projector. VRex has also rendered and multiplexed images in true 3-D from scanning electron microscopes, scanning probe microscopes, and magnetic resonance imaging and computed tomography scanners. Images from the National Library of Medicine's Visible Human data set as well as other anatomy images have been displayed in stereo with the VRex system, again, using passive glasses.

Computer-aided Diagnosis

By combining expert system databases with parallel processing and neural net software, one can harness the speed of computers to examine complex processes and speed decision making. Computer-aided diagnosis (CAD) will not replace physicians, but it can expedite time-consuming tasks and raise levels of confidence in the decisions made. CAD is being built into several digital mammography systems now under development. The Food and Drug Administration recently ruled favorably on a CAD algorithm for cervical cancer detection, a cytology task performed by technicians. Pattern recognition, whether for images or data patterns, is a powerful tool whose time has come.

Strengths
Computer-aided decision-making can save time, discern patterns, extrapolate data for simulations, and help to predict outcomes.

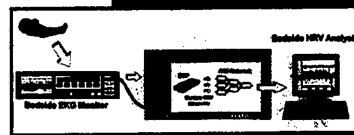
Limitations
CAD is subject to the "garbage-in, garbage-out" rule of computer science and is only as accurate as the software author and user.

Expert Systems Predict Disease Development

BMDO Technology Background

Funding from the BMDO SBIR program advanced the development of expert system software that has gained industry-wide recognition in the field of risk management. Called AIM® StatNet™, the software was developed by the AbTech Corporation (Charlottesville, VA). StatNet™ received PC Week's highest performance rating when contrasted with three other comparable, commercially available software packages.

StatNet™ has numerous medical applications in areas as diverse as audiological testing, neonatal assessment, and prediction of coronary artery disease progression.



▲ Online, real-time heart rate variability monitoring and analysis system.

How It Works

The software consists of machine learning algorithms and modeling techniques that merge the neural network concept with advanced statistical techniques. This combination produces a software tool exponentially more powerful than either precursor. StatNet™ automatically determines the network structure, node types, and coefficients of a model from a user-provided database. It then displays a graphical representation of the completed model. This graph illustrates the relationships among variables and gives the user insight into which variables are important. StatNet™ also provides evaluation results using independent testing data and generates C source code of the network equations.

Potential Use to Medicine

For hearing tests, StatNet™ was used to enhance an automated testing system that drew on a large database of possible test patterns. The number of parameters involved in hearing evaluation had grown too large for conventional statistical techniques. Using StatNet™'s unique statistical network approach, development time for this sophisticated diagnostic system was reduced by 60 percent. Integration of new rules into a growing database was also simplified.

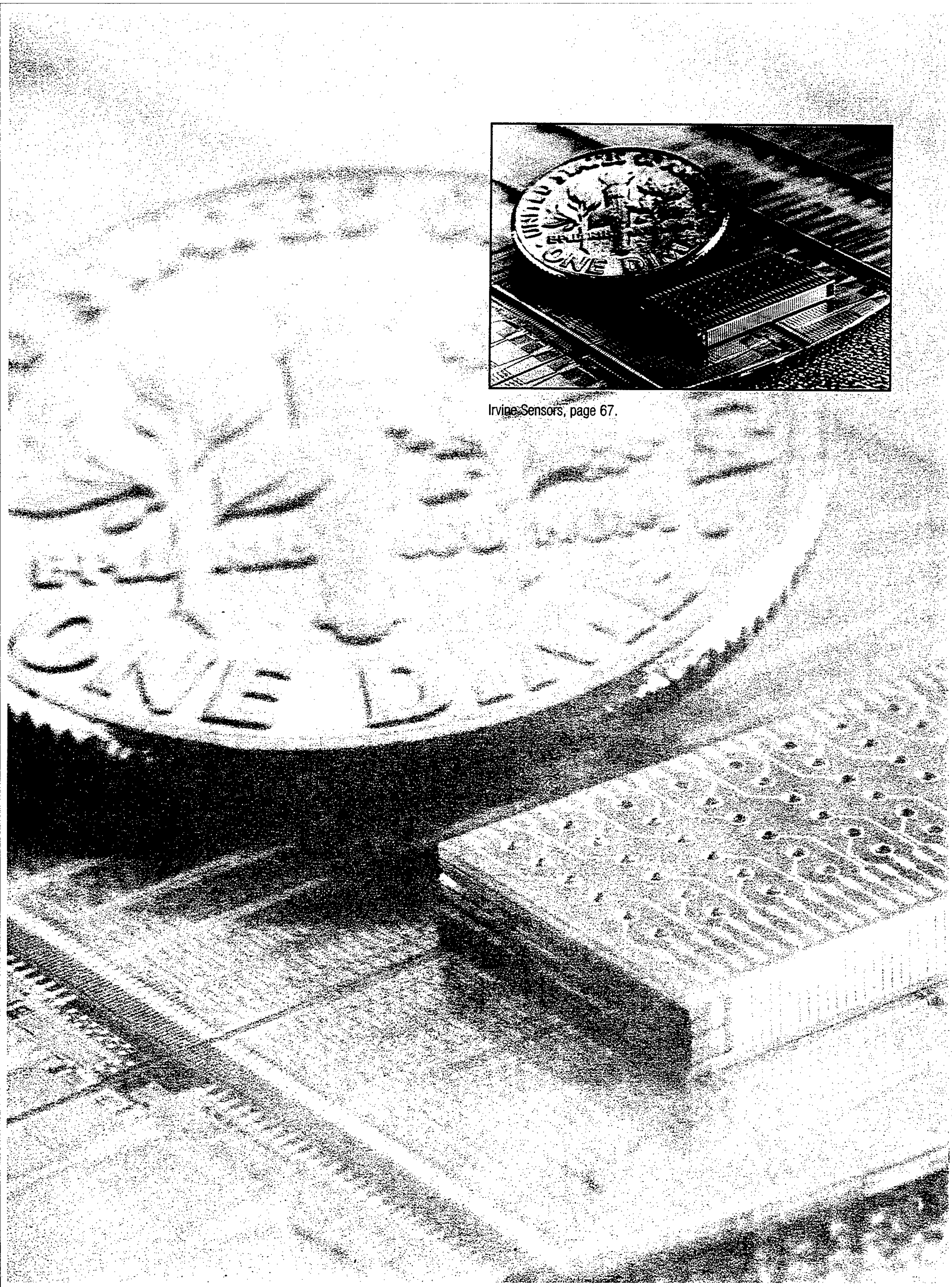
In neonatal assessment, StatNet™ has incorporated heart rate variability data in order to predict the probability of sepsis development in premature newborns. A number of researchers have hypothesized that a decrease in heart rate variability is predictive of many types of adverse conditions. By connecting infant electrocardiogram (EKG) data to a computer system using StatNet™ algorithms, researchers at the University of Virginia at Charlottesville are collecting data and "training" a diagnostic system to look for early warning signs of patient distress. Because sepsis (bacterial infection) can make premature newborns gravely ill in a very short time, this system can help doctors intervene before infection is too severe to combat. Nearly one-third of neonates who develop sepsis die of the disease.

StatNet™ is also being used to predict outcomes for patients with cardiovascular disease. Drawing on data collected from treadmill tests, EKGs, and thallium imaging techniques, StatNet™ helped to evaluate degrees of abnormality for each of 13 assessment variables and to predict probability of myocardial infarction or cardiac death. Based on follow-up studies of 440 patients, monitored for an average of 4 years, researchers were able to use patient data to train a computer network to recognize warning signs of cardiac disease progression. The trained network was found to predict adverse events with a 92 percent accuracy rate.

StatNet™ is a complete software package that is readily available and can be used to model financial data, predict marketing results, perform pattern recognition, and manage health care databases.

Product Status and Availability

StatNet™, a complete software package that is readily available, can be used to model financial data, predict marketing results, perform pattern recognition, and manage health care databases.



Irvine Sensors, page 67.

Enabling Technologies

Modern medical technology is a complex organism of diverse, interacting components, much like the creature whose health it addresses. Some of these components are highly visible, while others are obscure. This section contains brief discussions of some of the BMDO research that has the potential to contribute to the growing and changing health care industry. Although the original conceptions behind the technologies described are decidedly nonmedical, these innovations may someday play a part in information infrastructure, advanced electronic devices, image displays, and data transmission, all of which can and will have some impact on biomedicine. In some cases, the technologies discussed here are in their infancy. In many instances, a concerted commercial effort has not yet been connected with the technology.

This section will be noticeably different in format than the preceding sections. We present these brief items as food for thought.

Materials

As discussed in previous sections, infrared (IR) sensing can play a role in noninvasive diagnostics. BMDO has long pursued material advances to develop rugged, low-cost, highly sensitive detection technology for use in air, space, and terrestrial viewing. Some of the advances described here have not been integrated into medical devices, but they are included for their potential use in biomedicine. Also detailed here is a high-temperature semiconductor coil for magnetic resonance imaging (MRI).

New Materials Bring New Capabilities

■ **Advanced Silicon Materials (Moses Lake, WA)**
This company produced ultrapure silicon that can improve very long wavelength IR (17 microns) detection by up to 25 percent and increase operating temperatures by 40 percent. When this material was developed in 1990, its cost was 50 to 80 percent lower than prevailing prices. This BMDO-funded technology has been used by several organizations, including Wright-Patterson Air Force Base, to produce improved IR detectors. Advanced Silicon Materials produces ultrapure silicon for the commercial market.

■ **Amber (Goleta, CA)**
Amber developed indium antimonide detectors for BMDO sensors programs. These detectors are used in an Amber product called Radiance 1, an IR camera. Indium antimonide is the medium of choice for detection of middle wavelength IR (about 4 microns), and, when cryocooled, it provides optimum signal-to-noise ratio. Amber's cryocooling system does not require nitrogen dewars.

■ **Superconductor Technologies, Inc. (STI; Santa Barbara, CA)**
STI has received several SBIR grants to develop high-temperature superconducting (HTS) materials. The company has developed an HTS coil that can be used to produce MRI images with 1.5 to 2.5 times better resolution than present technology allows, in about one-fourth the time. STI has also developed a lightweight MRI unit that can be used on the battlefield.

Readouts, Image Processing, Visualization Technologies

Accurate representation of anatomy for surgical intervention, data processing in the hospital accounting office, and clear images for radiological screening and MRI all depend in part on visualization technologies. Medical training can also benefit from advances in representational learning tools, without (as a wag has put it) the "olfactory stimulation" of the laboratory. Recently, the Visible Human, a collection of cadaver sections imaged with MRI, computerized axial tomography, and photographic slides, was made available for viewing on the Internet. This small demonstration is just one of the endless possibilities for education and information dissemination offered by visualization technologies. The underpinnings of these technologies are electronic memory and representation. In this subsection, we examine BMDO efforts that can help to advance image processing, readouts, and visualization.

High-Speed Data Processing Stacks Up

■ Irvine Sensors Corporation (Costa Mesa, CA)
Irvine Sensors developed smaller, faster electronic processors by using three-dimensional chip architecture, a technology that shortens the length of chip interconnections. The company used its patented technology to develop "Smart Sensors" for BMDO infrared imaging applications. Irvine Sensors can stack a detector array, amplifier circuits, and signal processing electronics in a sensor module that may be applicable to medical image processing. Chip stacking can also be used in neural networks and memory storage; this development effort was also funded in part by BMDO. Irvine Sensors manufactures a memory component called Memory Short Stack™ as part of a joint manufacturing alliance with IBM.

■ Kensal Corporation (Tucson, AZ)
Kensal has developed processing algorithms that can convert planar, scanned image data into a three-dimensional workspace. This technique can be used to process "stacks" of tomographic data produced by radiologic, ultrasonic, or magnetic resonance imaging. Kensal demonstrated proof-of-principle with the help of a BMDO SBIR contract. A commercial software package called Triakis resulted from implementation of these algorithms.

Kensal's algorithms have been tested in the areas of radiology, pathology, cytology, and tissue morphology. In one case, these algorithms have helped to distinguish malignant from nonmalignant cells.

■ Lawrence Livermore National Laboratory (LLNL; Livermore, CA)
In addition to its research with Fischer Imaging in digital mammography, LLNL is using an image scanner, available through DuPont for defense purposes, to develop algorithms that will flag microcalcifications in mammograms. These tiny flecks of calcium can be a warning sign of breast cancer and are hard to see with the unaided eye. Researchers hope to use these algorithms as a diagnostic tool and to expand their use into other areas such as dentistry.

■ LNK Corporation (Riverdale, MD)
LNK has developed a hybrid of neural network and expert systems software that is able to fuse data from multiple sensors to track and recognize objects of interest. The software can provide real-time information about multiple, moving targets against a cluttered, moving background. Although LNK designed this technology for the BMDO SBIR program with defense interests in mind, these interests translate well to the complex pattern recognition that is needed in diagnostic imaging and image-guided therapy. LNK markets its product, Image_Lib, as an image processing and analysis toolbox that can be run on a commercial parallel processor. The company has also worked with Adaptive Solutions, Inc., (Beaverton, OR) to speed the toolbox's operation by enabling it to run with the CNAPS® parallel coprocessor, which is one of the least expensive parallel processors.

■ NETROLOGIC (San Diego, CA)
NETROLOGIC developed neural network, wavelet, and genetic algorithms for improved image processing as part of a BMDO Phase I SBIR. Surveillance, target acquisition and sequencing, and data fusion were among the areas addressed; NETROLOGIC has also explored some medical imaging applications of this technology.

■ Space Computer Corporation (Santa Monica, CA)
Space Computer Corporation developed a high-speed image processor through a BMDO SBIR contract, originally for space-based imaging. The processor can achieve peak throughputs of 2 billion floating point operations per second (FLOPS). As a parallel processor, it is suitable for high-speed medical image processing.

Displays

Display technology comprises electro-optics, light-emitting diodes (LEDs), field-emission displays, flat panel displays, and vertical cavity surface-emitting lasers. Together, these technologies have been a great improvement over cathode ray tubes and other components of video screens. Low power consumption, high resolution, and compactness are just some of the features that can be incorporated into medical displays as the field matures even further.

A Spectrum of Visual Technologies

■ ACT Research Corporation (Cambridge, MA)

Through a BMDO Phase I SBIR, ACT Research has developed a means of displaying three-dimensional (3-D) images that can be viewed from all directions and that requires no special glasses. ACT's 3-D display technology is suitable for commercial workstations, air traffic control systems, desktop computers, and multiple player video games. Its software will also be designed to work with existing 3-D graphics tools. ACT plans to continue development of this display through a Phase II SBIR from the Advanced Research Projects Agency. The company's technology has the potential to meet the growing demand for 3-D training modules and realistic representation of solid objects. This display can be used, for example, to accurately site tumors for radiation therapy. To prevent harm to healthy tissue, X-ray beams must be precisely aimed, and volumetric images can provide the best spatial information in such cases.

■ Advanced Technology Materials, Inc. (ATMI; Danbury, CT)
■ Cree Research, Inc. (Durham, NC)

Blue LEDs have come a long way in recent years, with progress seen in increased brightness and extended lifetimes. Blue has long been considered the "missing" color needed for full-color LED images. Both Cree and ATMI are leaders in this technology, which is based on silicon carbide and gallium nitride substrates. Cree has been selling a blue LED for several years and recently introduced a brighter blue LED into the marketplace.

■ Displaytech, Inc. (Boulder, CO)
■ Kopin Corporation (Taunton, MA)

Both Displaytech and Kopin have made advances in flat panel display technology through BMDO SBIR funding. Kopin makes a small format display (less than 1.5 inches) with its proprietary wafer engineering technology. This active matrix liquid crystal display (AMLCD) features higher resolution and greater speed than conventional AMLCDs.

Displaytech uses a ferroelectric liquid crystal layer over a silicon chip that contains a miniaturized high-resolution pixel array. This technology promises full-color, video-rate displays with a resolution of 2,000 x 2,000 pixels, optical data rates in the gigabyte-per-second range, and low production costs.

■ North Carolina State University (NCSU; Raleigh-Durham, NC)
■ Eagle-Picher (Miami, OK)

NCSU and Eagle-Picher have established formal programs to commercialize long-lived, blue and green LEDs based on II-VI double heterostructures, such as zinc tellurium selenide, grown by molecular beam epitaxy. BMDO helped fund the effort at NCSU. So far, the project has produced the brightest green LED ever, as well as a blue LED based on the same family of materials. In addition, Eagle-Picher demonstrated the first ever blue and green lasers using the homoepitaxial structure of ZnSe (zinc selenide) on ZnSe. These advances are important for display technology as well as read/write capabilities for achieving greater storage density in optical storage media.

■ SI Diamond Technology, Inc. (Houston, TX)

SI Diamond Technology, Inc., is developing a field-emission display that exploits the favorable properties of diamond cold cathodes, which emit electrons at much lower power levels than other materials. Unlike virtually any other cathode material, diamond is not easily poisoned by exposure to air, water, and other environments. In addition, field-emission displays (whose traditional strength has been ease of manufacture) that use diamond cold cathodes could produce images of equal or better quality than AMLCDs, today's leading flat-panel display technology. In the medical imaging arena, SI Diamond has teamed with Fischer Imaging Corporation (Denver, CO) to develop a flat-panel display system for digital mammography.

Transmission

Telemedicine requires transmission of huge amounts of data. The data must be transferred and processed quickly, and medical images must suffer no loss in information content.

Both materials and methods affect the development of real-time telemedical capabilities, which include miniature light sources, transmission media, and data compression techniques.

Lasers and Fibers Light Up Transmission Tasks

■ **HNC (San Diego, CA)**
At HNC, BMDO funded a data compression technique that could allow faster transmission of medical images. The technique uses a neural net filter to produce high-resolution images at a 100 to 1 compression ratio, while producing a clearly recognizable image. Current commercially available technologies compress data at a 10 to 1 ratio.

■ **Micracor, Inc. (Acton, MA)**
Micracor manufactures microchip lasers that will be important components of future fiber-optic data transmission networks. Micracor now markets a line of miniature, diode-pumped, solid-state lasers called MicraChip® that are used in communications, cable television, optical disk, display, and printer applications. Tunability of these lasers allows the transmission of multiple channels for high-data-rate image transmission.

■ **Optical Concepts, Inc. (Lompoc, CA)**
■ **Vixel Corporation (Broomfield, CO)**
■ **University of California at Santa Barbara (Santa Barbara, CA)**
Optical data transmission is also facilitated by vertical cavity surface-emitting lasers, or VCSELs. Because VCSELs emit laser beams perpendicular to their surface, they have the ideal geometry for stacking side-by-side in arrays. VCSELs are also 20 to 50 times smaller than edge-emitting diode lasers and are ideal for inputs to fiber-optic cables. BMDO has funded VCSEL research at Optical Concepts and Vixel, as well as at the University of California at Santa Barbara. Vixel currently markets the world's only commercially available VCSEL product, a two-dimensional array sold under the trade name LASE-ARRAY™. Optical Concepts has a patent pending for a long-wavelength VCSEL that operates at room temperature.

■ **Optigain, Inc. (Peace Dale, RI)**
Many fiber-optic transmission systems require optical amplifiers to help propagate signals through a cable. To meet this need, Optigain has developed active fiber amplifiers that have broad application in fiber-optic data transmission. BMDO helped to fund development of these active fiber amplifiers, which are made by doping silica or heavy metal fluoride glass hosts with a variety of rare earth elements. The doped fiber becomes optically active when pumped with laser light.

■ **Optivision (Davis, CA)**
Optivision developed a high-speed fiber-optic bus extender that allows two workstations to transfer data between each other nearly as fast as they can transfer data internally. The bus extender, which would be useful for transferring medical images through local- and medium-area networks, has demonstrated a transfer rate of 7.5 megabytes per second (MB/s) between workstations 2 km apart. Researchers believe that with current technology, this rate can easily be increased to 15 MB/s and eventually to 30 MB/s between stations.

■ **Physical Optics Corporation (POC; Torrance, CA)**
Using polymer waveguide technology funded by the BMDO SBIR program, POC has developed compact devices for fiber-optic transmission known as FiberView links. These links provide a transmission bandwidth of 10 MHz and a signal-to-noise ratio of more than 56 decibels. The 15 in^3 device can operate at wavelengths of 850 or 1,300 nm and is compatible with fibers of 50, 62.5, or 100 microns in diameter.

POC has also developed an adaptive bit error rate measurement system that is more accurate, faster, cheaper, and more adaptable than today's measurement systems. These advantages will be important in the transmission of medical imagery, where bit errors can have dramatic effects on diagnosis.

Data Storage Materials

Medical data storage requires a large electronic memory for archiving medical images, patient histories, and physician's notes. Large hospitals and health maintenance organizations, serving hundreds to hundreds of thousands of people, can benefit greatly from improvements in data storage and management. Patient satisfaction and rapid diagnosis derive from speed, accuracy, and accessibility to crucial medical documents and images.

Any system that works with digital imagery requires high-density data storage technology to archive large databases of images. Because of its large storage capacity and fast access speeds, optical data storage techniques have received considerable attention from BMDO. Some of the optical storage media developed for BMDO can store billions of bits of data in a volume no bigger than a sugar cube; in addition, BMDO has funded several short-wavelength lasers that can write more data onto conventional materials.

Room Enough for Information Overload

■ Oak Ridge National Laboratory (Oak Ridge, TN)

A new technique developed at Oak Ridge National Laboratory offers an answer to the demand for increased storage density. Surface-enhanced Raman optical data storage is based on a technology that detects the optical signature of laser-excited molecules. This data storage method involves the alteration of molecules that are embedded in a polymeric or silver-colored disk. A laser is used to "write" information on a disk, on which the optically altered molecules and unaltered molecules serve as "bits." The normally weak Raman signature of each molecule is amplified or enhanced by the substrate of the storage disk, such that the signature can be read by a signal detector.

Of special interest is a cousin to this technology that has exciting applications in the field of DNA hybridization. SERS, or surface-enhanced Raman scattering, can eliminate radioactive markers in nucleic acid hybridization technologies. Using the SERS technique, experiments have shown that DNA-DNA hybrids can be visualized without radioisotope tagging. Reduction of radioactive waste and speeding up hybridization results are two distinct advantages of this technique. Among the many applications are Southern blots, genetic sequencing, and chromosome analysis.

■ Optex Communications Corporation (Rockville, MD)

Electron-trapping (ET®) materials have the unique ability to store electrons in a stable atomic state for long periods after they have been excited by incident light, which makes them ideal optical data storage materials. Quantex Corporation (profiled elsewhere in this report) has spun off another company, Optex Communications Corporation, to market high-density data storage devices that use these materials. So far, Optex has raised $20 million in equity investment for the development of data storage devices that can store the equivalent of 30 compact disks on a single 5¼ inch disk. Optex has also received a 1992 Advanced Technology Program award from the National Institute of Standards and Technology to develop an erasable optical disk drive suitable for digital video recording.

■ Optitek (Mountain View, CA)

Optitek plans to develop Stanford University's lithium niobate technology (see below). Its first targeted market will be video-on-demand in which customers could download videos from a central library over fiber-optic links. The company is also looking at broader needs such as data archiving of medical and government records and other areas where massive digital storage is required. Optitek is a spinoff company from Stanford University's Center of Nonlinear Optical Materials.

■ Reveo, Inc. (Hawthorne, NY)
■ SPARTA, Inc. (Lexington, MA)

The BMDO SBIR program sponsored research on two other optical data storage technologies: one at SPARTA and the other at Reveo. SPARTA's system uses spectral hole burning (SHB) materials to store as many as 10^{12} bits of information per cm^3, a figure that theoretically could reach 10^{15} bits per cm^3. While current designs use an SHB material that must be cooled to 4 degrees Kelvin to provide long-term data storage, SPARTA researchers are trying to identify SHB materials that do not require cryogenic cooling. Reveo's technology uses multilayered cholesteric liquid crystals to provide high-density data storage; the company plans to market multilayered CD-ROM devices based on this technology in the near future.

■ Stanford University (Palo Alto, CA)

Using another material, a lithium niobate photorefractive crystal, Stanford University has demonstrated the first fully automated digital holographic data storage system. A research team led by Professor Lambertus Hesselink used the system to store a picture of Leonardo da Vinci's Mona Lisa. Although still years away from a product, his work could lead to systems that store 10 to 100 times more data and provide 1,000 to 10,000 times faster data access speeds than present systems.

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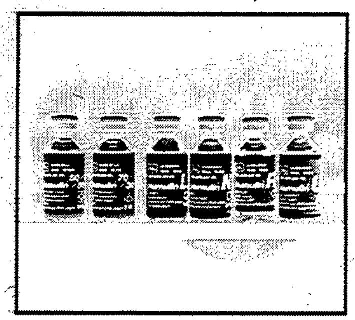

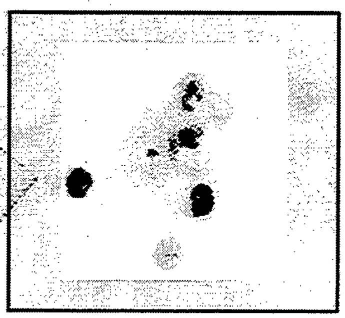

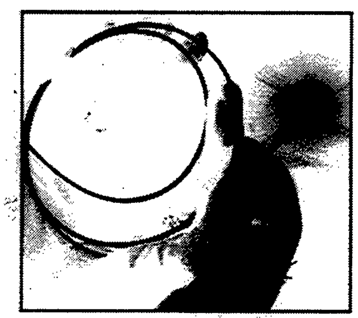

▲ Top: Rio Grande Medical Technologies, page 53.
Center: Ciencia, Inc., page 51.
Bottom: Fiber Optics, page 37.

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